Early Detection of Colorectal and Gastric Cancer

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1988

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SUMMARY

The roles of a self-administered symptom questionnaire, four tumour markers (carcinoembryonic antigen, alpha-1-acid glycoprotein, C-reactive protein and gamma glutamyl transpeptidase) and faecal occult blood (FOB) testing were investigated for their individual and combined ability to detect colorectal and gastric cancer in both asymptomatic and symptomatic populations at an early stage.

One thousand and eighty two individuals from six general practices were invited to participate in cancer screening either during a consultation with their general practitioner or by letter of invitation to attend the practice for a screening appointment. Seven hundred and twenty four subjects accepted and 683 returned completed FOB's. Twenty asymptomatic subjects (2.9%) had a positive FOB and on investigation two individuals were found to have cancers of the colon (1 Dukes' stage A and 1 stage B) and 3 further individuals had adenomatous polyps greater than one centimetre in diameter detected.

A symptom questionnaire was specifically designed for this study and a pilot study comprising 144 subjects was performed to determine the validity of the questions. Three questions were shown to be ambiguous but the responses obtained for the remainder were found to compare favourably with those gained by a consultant clinician. In the main screening study the prevalence of gastrointestinal symptoms was high but on review only 38 of these individuals were felt to be harbouring previously unsuspected disease. Upon subsequent investigation although benign pathology

was identified no neoplastic disease was found. These findings preclude the use of a simple symptom questionnaire in population screening for colorectal or gastric cancer.

Compliance for FOB screening in this country is on average 33% for a simple postal approach. Compliance was increased to 77% by direct invitation from the subjects own general practitioners, as part of their routine consultation, compared to 50% for a written invitation. Once enrolled 90% of the study group returned a completed FOB kit demonstrating that this test can be performed by the general public if adequately promoted.

The attitudes of the population offered screening were assessed using a questionnaire. Differences in beliefs concerning the value of preventive medicine, and attitudes to cancer and illness were found that significantly distinguished between compliers and non-compliers. This could have a bearing on how medical educationalists and screening organisers should promote future programmes.

Multivariate analyses were applied to the symptoms and tumour marker values of a symptomatic population to predict the risk of cancer in a given individual. The combination of both approaches gave in a prospective group a sensitivity for cancer of 88.5% and a specificity of 89%. Using log likelihood ratio analysis for dyspeptic symptoms alone, a scoring index has been derived that can predict the presence of gastric cancer as accurately as a clinician. This index has in a prospective study of 300 consecutive dyspeptic subjects a sensitivity of 93% for cancer, a specificity of 89% and a positive predictive value of

33.3%. This approach can readily determine 'risk' of cancer and therefore priority for investigation in a symptomatic individual.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor G.R. Giles for his support, guidance and constant interest in this work.

I also wish to thank Professor E.H. Cooper in the Unit for Cancer Research, University of Leeds, for his scientific advice during this study.

I am also indebted to Mr. R. Marshall and Miss B.J. Unwin for their advice on the statistical analyses used in this study and also to Mr. D. Brown for his technical assistance with the biochemical measurements.

To Mrs. I. Poole goes my gratitude for her invaluable help in the preparation of this thesis.

I owe a debt of thanks to both the Yorkshire Regional Cancer Organisation and the Yorkshire Cancer Research Campaign for the financial support I have received while undertaking this work.

Finally, I would like to thank Pamela, my wife, for all her support, encouragement and patience whilst I wrestled with the writing of this thesis.

CHAPTER 1

Introduction and Historical Review

The Problem

In 1979, 124,638 people died of cancer in England and Wales. Of these, 16,583 were due to cancer of the colon and rectum and 11,205 deaths due to gastric cancer. Whilst the number of cancer deaths has shown a slight decline for gastric cancer and a slight increase for colorectal cancer, the overall death rate of 24 and 35 per 100,000 respectively has altered little over the past 25 years (OPCS mortality statistics, 1981). The overall incidence for colorectal cancer in Great Britain is one of the highest in the world.

The 5 year survival figures for both cancers appears steady over a similar period. For gastric cancer, the overall survival rate in the period 1938-1949 was 5.6% in 375 cases (Swynnerton and Truelove, 1952); in the period 1950-1953, the crude 5 year survival for 4274 patients was 4.9% (Brookes et al, 1965) and finally in the decade 1960-1969 Fielding et al (1980) reported a 5 year survival rate in a series of 13,228 patients in Birmingham of 3.7%. A similar pattern is noted when considering colorectal cancer, where the Birmingham Cancer Registry reported a 5 year survival of 22% for rectal cancer and 21% for colonic cancer during the decade 1950-1959 (Slaney, 1971). These survival figures were unchanged during the subsequent decades (Slaney, 1978) and Clarke et al (1980) reporting their series of 443 patients studied in the 1970's found an overall survival of 27%. These survival figures for the two commonest gastrointestinal cancers are extremely disappointing in an era which has seen a revolution in diagnostic techniques, improved radiodiagnosis and remarkable improvements in operative survival.

The Solution

Although the overall prognosis for colorectal and gastric cancer is poor , certain patients do have prolonged survival following treatment. The clearest prognostic determinant for all cancers is the pathological stage at the time of therapy. Thus for colorectal cancer confined to the mucosa and muscularis propria the 5 year survival may be 65% - 94% (Gilbertsen et al, 1980; Gill and Morris, 1980). Similarly, for gastric cancer confined to the mucosa and submucosa the 5 year survival may be between 57% - 68% (Fielding et al,1980; Green et al, 1981). Unfortunately in the United Kingdom the number of early gastric cancers (EGC) confined to the mucosa and submucosa is between 0.7% - 10% (Fielding et al, 1980; Evans et al, 1978). The number of Dukes' Stage A cancers (Dukes, 1932) identified in recent series was 3.7% in the Nottingham hospitals (Holliday and Hardcastle, 1979) and 5.7% in the John Radcliffe Hospital, Oxford (Gill and Morris, 1978).

It is clearly desirable that the ratio of early stage cancers to advanced lesions is increased. This may be achieved by means of screening programmes or by more efficient recognition of these cancers in a symptomatic patient.

What is Screening

Screening has been defined as "the presumptive identification of unrecognised disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment." (Gnauck 1980).

It should be noted that, by this definition, unrecognised symptomatic as well as presymptomatic disease is included, and that the object of screening is "early disease detection" and to bring these subjects to treatment (Wilson and Jungher 1968).

The success or otherwise of a screening programme is dependent upon the accuracy of the screening agent itself, the acceptability of the test to the population to be screened, the population's participation in screening, the cost of establishing and maintaining the programme and the success of treatment available for the disease under investigation when treated early rather than late.

The cornerstones of screening are clearly the validity of the agents used and the populations compliance with the screening invitation. These will be discussed in detail in subsequent sections. However, to establish a few definitions that will be raised in the results and discussion the measures of validity for any test will now be described.

The ideal test will separate those who have the disease in

question from those who do not. The ability of the test to detect the disease is determined as sensitivity i.e. the true positive rate, whilst any cases missed will be the false negative rate. In practical terms the actual value of the false negative rate may not be precisely known since it would be impracticable and probably unethical to investigate all patients with a negative test to establish this value. The ability to classify those as not having the disease is termed specificity. Those subjects misclassified as harbouring the disease by the test and are subsequently found on investigation to be free of disease are said to have had a false positive result. This figure will be known for all screening programmes and any test with a low specificity will subject many people to unnecessary investigations which may have an attached risk e.g. colonoscopy, with time off work for the subject and an additional running cost for the programme with no apparent gain.

When comparing the impact of different screening tests for the same disease the predictive yield for the tests may be of value. The predictive yield is that fraction (%) produced by the number of cases detected divided by the number of subjects investigated as a result of a positive test. The yield is dependent on the validity of the test, the pre-existence of the disease and the quality of the follow-up examinations (vide infra).

Compliance among asymptomatic patients who are the target population must be sufficient to justify the cost of the programme i.e. must be at a level to effectively alter the natural history

of the disease in question.

There are many pitfalls to the understanding of the biases associated with and inherent in screening programmes but these are beyond the scope of this research. To introduce the reader to the subject of early detection of colorectal and gastric cancer, I have followed Kipling's example of using his "6 wise serving men, honest and true, the what, when and where and the how,which and who" to review the state of the art.

Why screening?

Those who are in favour of screening for cancer and in particular for colorectal and gastric cancer use survival statistics such as reported in the section entitled 'The Solution' to support their argument. They may also argue that there is no really viable alternative to screening to reduce the mortality of these two cancers. Two reasons cited to support the need for screening or earlier detection are :

A Failure of primary prevention (epidemiology) to identify the cause of cancer.

B Failure of current therapy to reduce mortality.

Each concept will be discussed in turn.

A. Failure of Primary Prevention (Epidemiological approach)

Epidemiology may be defined as the identification of the causes of human cancer with a view to their prevention by searching for, and studying, groups of individuals with different incidences of cancer. Much of our knowledge of cancer results from epidemiological study and over 30 causes, about half occupational in nature, the remainder being social or iatrogenic,

have been identified.

Some indication to the aetiology of large bowel cancer and gastric cancer come from the large geographical variation in incidences throughout the world. Japan and areas of South America have the highest incidences of gastric cancer in the world and yet have relatively low risk for colonic cancer. Conversely in Western Europe and the USA there is considerably higher risk of colon cancer than gastric cancer.

Migrant studies have also shown that when families move from high risk to low risk areas for gastric cancer, then the incidence of cancer drops to an intermediate level in the first generation and practically to the local level in the second generation (Haenszel and Kurihara, 1968). In colonic cancer the fall in risk appears to be more rapid (Buell and Dunn, 1965).

These studies favour environmental rather than genetic factors as being the principal cause of these cancers. Thus many studies have been undertaken to determine differences in diet, soil and water as causes of cancer.

The main aetiological factors currently favoured as being linked to gastric cancer causation are diet related. Lack of fresh green vegetables, pickling of food, high salt content in the diet and a deficiency of beef protein and milk products have all been implicated in the causation of gastric cancer (Hirayama, 1972). Unfortunately, no individual dietary item has been totally incriminated. The bacterial production of nitrosamine substances from food in the stomach has been raised (Hill et al, 1973) especially in the hypochlorhydric stomach (Ruddell et al, 1976).

This certainly has been reproduced in the animal models of Sugimora and Kawachi (1978) and has received support from the observation of high nitrate levels in the water of high risk populations in South America (Armijo, 1979).

The carcinogen promoting effect of salt and nitrosamines can be blocked by fresh vegetables containing Vitamins A, C and E (Kurechi et al, 1980; Walker et al, 1980).

The debate on large bowel cancer centres round the dietary contents of fat and fibre in the causation of this cancer. A diet high in fat increases biliary secretion of acid and neutral steroids and these steroids exert a promoting or carcinogenic effect on bowel mucosa (Reddy et al, 1980). The "low fibre theory" proposes that through a decrease in faecal bulk and transit time a low fibre diet leads to an increased concentration in the large bowel of carcinogens and other substances contributing to the development of a malignant tumour (Burkitt 1969; Modan et al, 1975; Reddy, 1981).

Unfortunately, when cohort studies have been utilised to test case - control studies for gastric and colorectal cancer, the results are often inconclusive or even conflicting in their support for various agents as being carcinogens. In an excellent review article Zaridze (1983) reveals how much conflict and difficulty there has been in the studies of the high fat, low fibre theories. Alderson (1982) in another review reports on the role of alcohol in the causation of large bowel cancer and states that in 13 case cohort studies for colorectal cancer, 3 reported an association with beer drinking, 4 found no appreciable effect,

2 found a negative effect and 4 made no comment.

Despite these problems of identifying causation or association with cancer, and failure to identify truly reversible causes of colorectal, gastric or even breast cancers, Doll and Peto (1981) claim that up to 75% of all cancers in subjects under 65 years living in the USA are avoidable.

However, amongst their recommendations lies reduction in the amount of hamburgers and ice cream eaten, stopping smoking and drinking and increasing the intake of vegetables containing Vitamins A,C and E with a large increase in dietary fibre. Such proposals are firmly shared by Bruce et al (1981), Nigro (1982) and McKenna (1983).

There are, however, several drawbacks to this approach. Firstly, the public has consistently shown its own thoughts on the merits and demerits of cigarette smoking. There is also the political delay in banning cigarette smoking when tax revenue and employment are important factors against too strong action. Secondly, even in this country, court cases are still ruling against fluoridation of water to prevent dental caries (Scott v Strathclyde Region, 1982).

Thus, with no foreseeable breakthrough in the identification and removal of the cause of colorectal and gastric cancer, it would seem other alternatives will be required to improve the fate of Westernized civilisations for some time yet.

B. Failure of Current Therapy

The failure to achieve 'cure' after apparently curative resections is a worry to all surgeons. This is further compounded by the fact that more than 50% of recurrences experienced in colorectal and gastric cancer are locoregional i.e. within the surgical excisional field (Colorectal: Cass, Million and Pfaff, 1976; Whittaker and Goligher, 1976; Gilbert, 1978; Olsen et al, 1980; Ras et al, 1981). Gastric: MacNeer et al, 1951; Berne and Freedman 1951; Iwanaga, Kagoma and Furukowa, 1978; Koga et al, 1978; Pichlmayr and Meyer, 1981; Giles and Donaldson, 1983).

The reasons for such failure of control may be inadequate surgery, or micrometastases at the time of surgery, both local and systemic. This has lead to the concept of adjuvant therapy with radiotherapy to the local field and/or chemotherapy for the systemic micrometastases.

Unfortunately radiotherapy, either preoperatively or postoperatively, has not shown great impact on reducing recurrences or prolonging survival in colorectal cancer (Hoskins et al, 1980; Duncan, 1985) unless high doses are used which inevitably produce considerable toxicity (Hoskins et al, 1980; Romsdahl and Withers, 1978). Similarly, preoperative (Hoshi, 1968) and peroperative radiotherapy (Abe et al, 1975) has been shown to be of little value in the management of gastric cancer. However, postoperative radiotherapy plus chemotherapy may have some value in the management of gastric cancer (Goffin and Machin, 1979).

The use of adjuvant chemotherapy has now evolved through

trials of single agents to measure a response, to combination therapy. Colorectal cancer has relied principally on 5 Fluoro-uracil (5FU) but experience with 5FU and FUDR in over 2000 patients has shown a less than 10% response (Grage et al, 1979; Higgins et al, 1976; Dwight et al, 1973; Grassi et al, 1977; Lawrence, Tery and Horsley 1975). Combinations of 5FU, Methyl CCNU and oral BCG are now under evaluation with encouraging results (Killen 1981; Panettiere and Chen 1981).

In the adjuvant setting for gastric cancer, single agents such as mitomycin C (Goto et al, 1977; Koyama, 1978 and Nakajima et al, 1978) have shown less than a 10% response. Schein et al (1982) however feel that gastric cancer is a chemosensitive tumour and that combinations of drugs which include Adriamycin may well be of value in the treatment of advanced gastric cancer and for the adjuvant setting.

It would seem apparent, however, that the spectacular successes that have occurred recently in the management of acute lymphoblastic leukaemia, testicular teratoma and Hodgkin's disease using combination chemotherapy will not be repeated for colorectal and gastric cancer. Thus whilst intense research is on-going into biological response modifiers (Carter 1980; Guillou 1987), radiosensitizers (Carter, 1982) and newer chemotherapeutic regimens there is little evidence to date of a significant breakthrough in the management and therefore survival in those patients whose cancer has breached the serosa or spread to the lymph nodes and who traditionally have been felt to be surgically curable.

Who should be screened?

Where the causative agent of a cancer is known but cannot be removed from the environment e.g. uranium in nuclear fuel reactor plants then the 'at risk' population can readily be identified and be subjected to routine screening. Where the cause is unknown those at increased risk should possibly be screened. For colorectal and gastric cancer, the causative agents have not yet been ascertained, but epidemiological studies have indicated certain individuals to have a considerably greater risk of developing these tumours compared to the remaining population. In these 'high risk' populations a programme of selective screening could therefore be effective.

'High risk' individuals for gastric cancer include those with Menetriers disease ; pernicious anaemia (Elsborg and Mosbech, 1979; Stockbrugger and Cotton, 1981); gastric polyps (Tomasulo, 1971; Niemark and Rogers, 1982; Kamiya et al, 1982); coalminers (Ames, 1983); chronic atrophic gastritis (Siurala et al, 1966; Sipponen et al, 1984), intestinal metaplasia (Iida and Kusama, 1982) and previous partial gastrectomy (Eberlein, Lorenzo and Webster, 1978; Hermanek and Riemann, 1982; Farrands et al, 1983; Schafer et al, 1983; Pickford et al, 1984). However, in terms of increased risk of gastric cancer arising in these patients compared to the general population the ratio is less than 2:1 for previous gastrectomy, atrophic gastritis and intestinal metaplasia making these fairly weak indicators of cancer risk for screening purposes.

For colorectal cancer, the risk groups can be divided into

those with a genetic predisposition and those associated with benign inflammatory conditions of the large bowel (ulcerative colitis and Crohn's disease, Weedon et al, 1973). The hereditary conditions include familial polyposis coli (Alm and Licznerski 1973), Gardner's syndrome (Gardner and Richards,1953), Cronkite-Canada syndrome (Cronkite and Canada, 1955), and the Cancer-Family syndrome (Lynch et al, 1981). The risk for cancer in these hereditary conditions appears to be 100% for familial polyposis coli, (Alm and Licznerski 1973) 66% for Gardner's syndrome, and unknown for Cronkite-Canada Syndrome. The cancer family syndrome may be associated with an increased risk of colonic carcinoma and also endometrial and ovarian carcinoma.

Individuals with the above conditions will be in the main already under surveillance by the medical profession and any members of the family of a recently diagnosed familial lesion should be screened. However, selective screening for these 'at risk' groups will only account for 10% of the cancer pool (Schottenfeld,1975) making little impact on the overall mortality of these cancers.

There remains however, one condition which appears to be a high cancer risk lesion said to be present in nearly all patients with colorectal cancer i.e. the colorectal adenoma (Grinnel and Lane, 1958; Kalus, 1972; Morson, 1974; Muto et al, 1975; Enterline, 1976). The risk of malignancy is directly related to the size, histological type and number of adenomata present. Approximately 1% of all adenomas under 1 cm in size undergo malignant change (Welch 1979; Morson 1974). Morson (1974)

further noted that with an increase in size the malignant potential rose; 50% of polyps over 2 cm in size showed histological evidence of carcinoma. Shinya and Wolff (1979) also found in a study of endoscopically removed polyps that 21% of polyps greater than 2 cm showed evidence of malignancy compared to 5% in those less than 1 cm.

Adenomas are histologically described as being tubular, villous or tubulo-villous (Morson, 1974). Muto et al (1975) described a 40% cancer presence in villous adenoma compared to 5% for tubular polyps, a finding also confirmed by Gillespie (1979) and Shinya and Wolff (1979).

Unfortunately, polyps tend to be relatively asymptomatic and therefore difficult to detect. Clearly any screening agent to detect colorectal cancer should also identify those larger polyps with a villous pattern to interrupt the polyp-cancer sequence (Morson, 1974; Gilbertsen and Nelms, 1977).

When do you screen?

The cancer mortality statistics show that colorectal cancers are relatively uncommon below 40 and rise dramatically in incidence from age 50 years. A similar pattern is seen for gastric cancer with a rapid rise in incidence from age 55 years (Mortality statistics, 1979).

It is reported that polyps tend to appear 5-10 years prior to cancers (Brahme et al, 1974) and that screening should therefore start 5-10 years before this rise in the incidence of colorectal cancers i.e. 40-45 years. The American Cancer Society has therefore proposed age 45 years as the time to initiate

screening. In this country Hardcastle (1980; 1983) has taken age 45 years as the cut-off age for screening. Lallemand et al (1984) have started screening at age 40 years and it may be that this early entry to screening was responsible for the poor yield of neoplasia in their large study.

For the purpose of this study age 50 years has been taken to indicate the lower age limit for screening in an attempt to raise the potential for detection of disease since the anticipated numbers entering the study will be small.

Which test?

Screening for colorectal cancer now principally relies on the faecal occult blood (FOB) test with the aid of sigmoidoscopy in many American centres but alone in the United Kingdom (Fig 1). Other methods including digital rectal examination, and rigid and flexible sigmoidoscopy have also been investigated but have not been adopted with the same enthusiasm as FOB testing.

Population screening for gastric cancer has received scant attention in Europe and North America due to the relatively low prevalence and falling incidence of this disease. Furthermore the only apparently reliable screening technique according to the Japanese experience appears to be endoscopy preceded by a 6 film barium meal study. The barium study identifies 85% individuals as requiring endoscopy and so a lengthy and expensive screening procedure is necessary (Micha et al,1985). Few Western countries would contemplate this approach so selective screening of at risk populations has been advocated including post-ulcer surgery

Fig 1 Screening for colorectal cancer using faecal occult blood tests and fibreoptic sigmoidoscopy.

patients. Even then there is controversy over this approach with Professor Langlands stating that in the United Kingdom there is little to be gained from it (Roberts and Langlands, 1983). One alternative approach has been suggested by Hakkinen et al (1980,1981), where population screening using gastric juice analysis was adopted with some success in the detection of EGC and advanced gastric cancer.

Tumour markers and symptom analysis have also been used to aid the earlier detection of these two cancers and will be reviewed now along with the above methods.

Faecal Occult Blood Testing

The concept of occult blood detection in the stool is generally credited to Von Deen, who in 1864 used gum guaiac as an indicator reagent (Irons and Kirsner, 1965).

Some 90 years later it has been appreciated that occult blood detection is dependent on the oxidation of a phenolic compound to a quinone structure, which in turn changes colour by an intermolecular reaction (Harvey, 1956). Hydrogen peroxide facilitates the oxidation process, which is catalyzed by the haematin component of haemoglobin or by naturally occurring peroxides and catalases in food. The resultant phenolic oxidation in the presence of a chromogenic indicator, e.g. guaiac, results in a blue colour (Fig 2). Benzidine and orthotolidine have also been used as colour indicators.

Commercial FOB Tests

The faecal occult blood test that is most frequently used in early detection of colorectal cancer is the Haemoccult test

Fig 2 Positive reaction to occult blood test.

(Norwich Eaton; Smith Kline Laboratories). This in common with Fecatest (Finpipette) uses guaiac as its chromogenic indicator. This review will concern itself principally with Haemoccult and Fecatest as they are to be used in the study.

Other commercially available tests use benzidine or orthotolidine as their indicators (Hemofec, Med-Kjemi A/S, HON, Norway; Hemotest, Miles Laboratories) but have fallen into disrepute for being too sensitive with high false positive rates (Morris et al, 1976; Irons and Kirschner, 1965; Cameron 1960). Furthermore, several chemical tests utilising benzidine and orthotolidine have been withdrawn because of their carcinogenic potential (Chester Beatty, 1966).

Immunological FOB tests

At the beginning of this study immunochemical detection of occult bleeding had been investigated by Barrows et al (1978) and Songster et al (1980), in the United States, by Vellacott, Baldwin and Hardcastle (1981), in this country and Williams et al (1982), in Australia.

Barrows and Songster with their team developed a radial immunodiffusion technique (Barrows et al, 1978) and applied this to 150 patients with diagnosed colorectal cancer (Songster et al, 1980). They found that the immunodiffusion technique was more sensitive than the guaiac test Haemoccult for all cases and for all anatomical sites. Thus overall the radial immunodiffusion technique detected 65% cancers compared to 40% cancers detected by Haemoccult. Haemoccult detected 50% right colon lesions, 34% left colon lesions and 29% rectal lesions, whilst the immunodiffusion

test detected 63%, 72% and 50% respectively. However, 29% cancers were missed by both Haemoccult and the radial immunodiffusion test. The restriction to the routine use of this test is the preparation time of 24-48 hours before reading the result.

Vellacott, Baldwin and Hardcastle (1981) developed a modified immunodiffusion technique using fluorescein-labelled anti-human haemoglobin binding antibody. Whilst the sensitivity of the test proved superior to Haemoccult it is not commercially available precluding any further investigation in this study.

Williams et al (1982) also modified Barrows' technique (1978) and found that the immunological technique was more sensitive in the detection of colorectal cancers and polyps (89% v 65% for Haemoccult) but that the immunochemical test was also subject to more false positives than Haemoccult.

Whilst this immunological approach will prove the most technically satisfactory FOB test no commercially available test that has been fully assessed, is yet available. Turunen et al (1984) however feel that they may have developed a much improved and easily performed immunochemical test.

"Normal" Gastrointestinal Blood Loss

The accuracy or 'sensitivity' of a chemical method for the detection of faecal occult blood can be compared with a "gold standard" method.

The development of radiochromium red cell labelling has produced such a 'standard'. It is a highly accurate and reproducible method of detecting occult blood loss. There is general agreement that 'normal' occult blood loss is in the order

of 0.5 - 2 ml blood per day (Roche et al, 1957; Ebaugh et al, 1958; Cameron 1960). Morris et al (1976) have used the convention of describing blood loss as mg haemoglobin per gram of stool and suggest an upper limit of 2 mg haemoglobin per gram stool per day as being normal.

An efficient FOB test should therefore detect blood only above these levels and when screening for colorectal neoplasia should not detect bleeding from upper GI disease (vide infra).

Ability of Haemoccult and Fecatest to detect blood in faeces

Ostrow et al (1973) were the first group to compare the sensitivity of chemical occult blood tests and the radiochromium red cell labelling method. This group found that where the stool under examination contained 5-10 mg Hb/gram stool then Haemoccult was positive in 50% of cases and where the stool contained more than 10 mg Hb/g stool uniformly positive results were obtained.

Similarly Morris et al (1976) investigated 39 patients with both Haemoccult and ^{51}Cr red cell labelled assay. Taking 2 mg Hb/g stool as the upper limit of normal they found that Haemoccult was positive in only 12% stools tested below this level. Stroenhlein et al (1976) also noted that Haemoccult was positive in 7.4% of 338 specimens where the level of blood loss detected by ^{51}Cr labelling was between 0.2 mg/day, rising to 67% with blood losses greater than 10 ml/day and 93% with blood losses of more than 30 ml/day.

Adlercreutz, Liewendahl and Virkola (1978) found that Fecatest could detect mean occult blood excretion of 2.5-3.0 ml or more /24 hour as determined by ^{51}Cr labelling techniques, using 24

hour homogenized faecal samples. Single homogenized faecal samples were positive to Fecatest only at levels of 4.8 ml blood/24 hours. Haemoccult was not positive until the blood loss/24 hours approached 10 ml.

The amount of bleeding from the upper gastrointestinal tract required to give a positive Haemoccult is much larger than from the colon. Subjects given labelled blood orally had only one positive reaction when 30ml were ingested (Ransom et al, 1980). Fecatest may be more susceptible however to upper GI bleeding giving a positive result. Parkins and Barrison (1981) detected positive Fecatest samples with as little as 5-10 ml of blood ingested.

In summary, Haemoccult will readily detect blood in faeces at a level of 10 mg Hb/g stool whereas Fecatest is more sensitive and will detect levels of loss of as low as 2.5-5 ml blood in 24 hr.

The sensitivity of Haemoccult and Fecatest in the detection of diagnosed Colorectal Neoplasia

In the previous section it has been shown that Haemoccult and Fecatest can detect occult bleeding above a 'normal' level. However, can these tests detect bleeding from a colorectal neoplasm and if so what is their sensitivity? Unfortunately many uncontrolled screening studies have been performed since Greegor (1971) first described the detection of asymptomatic cancers with Haemoccult without the true validity of the test being determined in established disease. Furthermore it would clearly not be practicable to endoscope or perform barium enemas on all those

participating in screening programmes to determine the false negative rate for the test. The true sensitivity can only be anticipated therefore by reviewing the literature for FOB testing in diagnosed colorectal neoplasia.

A number of these studies are now available to us (Table 1.1) and show a false negative rate for cancer ranging from 18-60%. However, in Songster's study (Songster et al, 1980) stool testing was only performed for one day, and since most authors follow Greegor's original suggestion of stool testing for 3 consecutive days one might anticipate that this high false negative rate could have been reduced by serial stool collection and testing.

Griffiths et al (1981) noted that 21 of 23 patients with a positive result had ulcerating lesions whereas all 5 cancers not detected by Haemoccult were not ulcerated. Leicester et al (1983) found that 22 of 25 (85%) patients with colonic cancer were detected by Haemoccult but that only 50% rectal cancers were thus detected. They suggested that there had been insufficient time for contact and mixing with stool for the rectal cancers to become Haemoccult positive.

It is also apparent that there is a low sensitivity (high false negative rate) for Haemoccult detection of adenomas of the large bowel. Macrae et al (1982) observed that only adenomas greater than 1 cm bleed and even then the false negative rate for polyps greater than 2 cm was 25%. Herzog et al (1982) studied 44 patients with colorectal polyps (34 polyps in the descending colon and rectosigmoid, 10 in the right colon) and noted that 25 (57%)

Table 1.1

False Negative Findings on Haemoccult testing in known colorectal neoplasm

Reference	Number cancers negative		Number polyps negative	
	n	%	n	%
Ostrow et al (1977)	3/7	42.8	3/6	50
Songster et al (1980)	90/150	60		
Schewe et al (1979)	30/84	36	31/53	58.5
Griffiths et al (1981)	5/28	18		
Doran and Hardcastle (1982)	15/50	30		
Macrae et al (1982)	13/42	31	20/28	72
Herzog et al (1982)			19/44	43.2
Leicester et al (1983)	9/37	24.3		
Farrands and Hardcastle (1983)	17/61	27.9		

overall were detected by Haemoccult. However, by considering site alone 86% of the left colon polyps were detected.

One British study reports the use of Fecatest in a symptomatic population. Farrands and Hardcastle (1983) noted that in 61 patients with proven colorectal cancer Fecatest was positive on 3 day testing in 55 patients (90.2%) that is a false negative rate of 9.8%. Haemoccult was also given to all these patients and on similar 3 day testing the false negative rate was 17 (27.9%) of 61 but fell to 9.7% on 6 day testing.

Causes of False Negative Responses to FOB testing in diagnosed Colorectal Neoplasia

Reduced to the simplest options the reasons for failure of Haemoccult to detect symptomatic diagnosed cancer may be either the cancer is not bleeding or the FOB test is not sensitive enough to detect the blood that is being lost.

As mentioned above Griffiths et al (1981) would favour the fact that non-ulcerating lesions are unlikely to be detected and the second option may be supported by Farrands and Hardcastle (1983) where Fecatest is more sensitive than Haemoccult in the ranges of 5-10 mg Hb/g stool lost. This lack of sensitivity for Haemoccult has already been reviewed (Ostrow et al, 1973; Morris et al, 1976).

The more scientific approach of Doran and Hardcastle (1982), Macrae et al (1982) and Herzog et al (1982), however, reveals the answer. These 3 groups investigated patients with known colorectal neoplasia, performed ^{51}Cr red cell labelling studies and analysed the Haemoccult findings with the blood loss

calculated by the radiochromium studies.

Doran and Hardcastle (1982) found large variations in the daily blood loss ranging from 0.00 - 74.7 ml/day, and that bleeding from individual tumours was found to be intermittent. In only 36 of 150 daily stool samples was the blood loss greater than 10 ml. Thus 15 of 50 (30%) cancers were undetected in 3 day testing with Haemoccult.

Macrae et al (1982) found that in a study of 46 cancers, bleeding was highest in ascending colon lesions, 9.3 ml/day, with losses of 1.5 ml/day for transverse colon, 1.9 ml/day for sigmoid colon lesions and 1.8 ml/day for rectal tumours. These patients collected samples on average for 5.8 days and for 11 patients at no time was Haemoccult positive.

Herzog and colleagues (1982) showed that polyps apparently bleed less vigorously, the mean blood loss per day for 34 left colonic polyps being 1.36 $\pm$ 0.14 (sd) ml/day and for right colonic polyps 1.28 $\pm$ 0.31 ml/day. They noted that in patients with left colon polyps whose faecal specimens contained 2.0 - 3.99 ml blood/day Haemoccult was positive in 86%, whereas right-sided lesions with equal loss yielded a positive test in only 26%. Thus in this study Haemoccult was able to detect low levels of bleeding, polyps were found to bleed little, and that detection of occult colorectal neoplasia was affected by anatomic site.

Other factors affecting the false negative rate apart from the low and intermittent nature of neoplastic bleeding include ingestion of Vitamin C (Jaffe, Kasten and Young, 1975; Garrick, Close, McMurray 1977) and dehydration (Macrae et al, 1982).

Whilst Macrae et al (1982) have noted improved sensitivity for rehydration of the Haemoccult slide, this whole question has been vexed with arguments in favour (Wells and Pagano, 1977) and against (Winawer et al, 1980). As the manufacturers do not recommend rehydration for the purposes of this study it has been deemed unnecessary.

Causes of False Positive Results on FOB Testing

Positive reactions to FOB testing in screening programmes range from 0.5-14% (Table 1.2) although the majority of workers have experienced positive rates between 2% - 5%. The false positive rates vary from 50% - 85% in these investigated cases.

The occult blood reaction is not specific for human haemoglobin but is affected by peroxidases and catalases in various foodstuffs e.g. fish, fresh fruits and uncooked vegetables (Macrae et al, 1982). The ingestion of these foodstuffs may therefore produce false positive results and so many investigators recommend dietary restrictions for the screened individual whilst the stool specimens are being collected.

The rehydration of the Haemoccult slide may increase the sensitivity of the test but may well lead to a fall in specificity (Wells and Pagano, 1977). Macrae et al (1982) have suggested that a strict diet excluding red meat may enhance the sensitivity of the test without increasing the false positive rate. As mentioned above this issue is contentious and the manufacturer's advice of no rehydration for Haemoccult will be adhered to.

Table 1.2
Selected Studies of Occult Blood Screening

	Reference	No enrolled	No accepted (%)	No positive (%)	No Cancer/Polyps	% enrolled with cancer
1.	1974 Glober and Peskoe	1,682	1,539 (91.5)	363 (23.7)	3 3	0.18
2.	1974 Hastings	3,450	2,625 (76)	159 (6.1)	5 0	0.14
3.	1977 Helfrich et al		8,930	157 (1.8)	3 2	0.03
4.	1977 Miller and Knight	2,332	2,278 (98)	64 (2.7)	1 7	0.04
5.	1977 Richardson	1,038	885 (85)	54 (6.1)	0 4	0.00
6.	1977 Winawer et al	6,597	5,307 (85)	64 (1.2)	7 23	0.13
7.	1978 Elwood et al	11,115	1,690 (15)	58 (3.4)	2 0	0.02
8.	1978 Fruhmorgen and Demling	6,007	5,016 (84)	136 (2.7)	13 83	0.22
9.	1978 Heeb and Ahlvin	5,740	3,956 (69)	79 (2.0)	5 5	0.09
10.	1979 Bralow and Kopel	3,798	3,008 (79)	329 (10.9)	7 11	0.18
11.	1980 Gnauck		16,100	531 (3.3)	75 106	0.47
12.	1980 Gilbertsen et al		48,000 (85)	864 (1.8)	72 271	0.15
13.	1980 Larkin	5,840	4,456 (95)	780 (14.0)	4 6	0.07
14.	1980 Winawer et al	13,127	9,709 (74)	243 (2.5)	43 -	0.44
15.	1980 Winchester et al	54,101	14,074 (26)	617 (4.4)	30 40	0.06
16.	1983 Sontag et al	13,522	2,964 (22)	135 (4.6)	14 44	0.10
17.	1983 Habba and Doyle	2,143	1,628 (76)	37 (2.3)	5 6	0.23
18.	1984 Elliott et al	5,012	3,422 (67)	99 (3)	12 21	0.41
19.	1984 Cummings	8,711	3,822 (44)	107 (2.8)	7 10	0.27
20.	1985 Kewenter et al	13,759	9,040 (66)	350 (3.9)	16 58	0.18
21.	1986 Klaaborg et al	8,000	4,705 (59)	78 (1.4)	10 39	0.21

Screening for Colorectal Neoplasia with Haemoccult and Fecatest

Boas is reported in 1901 to have emphasised the role of occult bleeding into the stool as indicating the existence of a gastrointestinal tumour (Irons and Kirschner, 1965), however, it took nearly 70 years before occult blood testing was deemed feasible following the efforts of Dr. David Greegor in Ohio.

The Breakthrough

Disenchanted with the unpredictability of guaiac, benzidine and orthotolidine testing (Hoerr et al, 1949; Mason and Belfus, 1952; Cameron, 1960; Irons and Kirschner, 1965) Greegor developed a stable guaiac preparation impregnated on electrophoresis filter paper, Hemoccult, (Greegor, 1967). By 1971, 900 asymptomatic patients had undergone occult blood testing, following dietary restriction, for 3 days. In these subjects, 5% had a positive Hemoccult slide and on subsequent investigation with sigmoidoscopy and barium enema, one per hundred screened had a colonic cancer detected (Greegor 1971). In 1972 he further reported the detection of 47 asymptomatic cancers detected as a routine office testing using Hemoccult.

As will be shown below, great interest was placed in Haemoccult testing and soon other guaiac impregnated paper FOB tests became commercially available (Fecatest, Hema-chek). By varying the concentration of guaiac peroxide then the sensitivity of the test can be varied thus explaining the difference in sensitivity between Haemoccult and Fecatest shown by Aldercreutz, Liewendahl and Virkola (1978).

Verification

Over the following decade many investigators have taken up with enthusiasm the Haemoccult test as a means of screening for colorectal neoplasia, and attempted to verify Greegor's findings.

The majority of these studies are uncontrolled, varying in size, population selection and dietary restriction, whilst only 3 large studies have been developed in a proper controlled fashion (Gilbertsen et al, 1980; Winawer et al, 1980; Hardcastle et al, 1983).

Uncontrolled Studies

Many studies have been performed throughout the world using Haemoccult to detect asymptomatic colorectal cancer. Table 1.2 lists the majority of large populations studied, along with the test positive rate, the number of cancers and polyps found, and the yield per 1000 screened.

Such studies have indeed detected asymptomatic colorectal cancers and polyps, and show earlier stage cancers than might be expected in routine practice (Goodman, 1977; Bralow and Kopel, 1979; Winchester et al, 1980; Larkin 1980; Sontag, Durczak and Aranha, 1983; Habba and Doyle, 1983). Where the data has been recorded it is clear that the ratio of early stage to advanced colorectal cancers is reversed with 143 of 194 (73%) of these cancers being either Dukes' stage A or stage B.

The positivity of Haemocult slides however ranges from 2% - 6% and of those the predictive yield of cancers for a positive test on subsequent investigation ranges between 2% - 14% (Miller and Knight 1977; Habba and Doyle 1983; Gnauck 1980). The yield of

polyps is higher in these studies than for cancer but the predictive value is only 20% maximum (vide infra).

The British experience of Haemoccult testing is very similar (Table 1.3). Professor Hardcastle in Nottingham pioneered Haemoccult screening in this country, selecting a small country town for his study. 1638 invitations were sent by post with an enclosed Haemoccult test to perform stool testing. 742 (45%) returned the FOB with 2 cancers and 4 polyps being subsequently detected.

Once again there is a range of positive responses from 1.5% - 5% for Haemoccult with both cancers and polyps being detected on subsequent investigation (Table 1.3). The cancers thus detected were 1 Dukes' Stage B and 3 C (Farrands et al, 1981), 2 Dukes' Stage A (Million et al, 1982), 1 Dukes' Stage B (Lallemand et al, 1984). Colonic polyps of greater than 1 cm in size were found in all studies and are included in the calculations of predictive yield of neoplasia.

Lee in 1983 has so far reported the only United Kingdom screening programme using Fecatest and had previously reported a comparison of Fecatest and Haemoccult in a mixed screening and symptomatic population study (Lee and Costello, 1982). In his occupation based screening study Lee (1983) recorded an overall positivity rate of 5.8% (140) of 2420 men and on subsequent investigation 5 cancers (2 Dukes' A; 1 Dukes' B; 2 Dukes' C) and 17 polyps were identified with 52 individuals having no lesion to explain their positive test. The predictive yield for a positive Fecatest was 15.7%.

Table 1.3

UK Screening Experience with Haemoccult

	No Pos HO n	%	No C/Polyps detected	Predictive Yield % neoplasia
Hardcastle et al (1980)	29	3.8	2/4	20.7
Farrands et al (1981)	124	5	4/8	9.7
Million et al (1982)	37	2.3	2/5	18.9
Silman et al (1983)	28	3.1	0/6	21.4
Hardcastle et al (1983)	77	2.1	12/27	50.6
Lallemand et al (1984)	26	1.5	1/9	38.6

In their hospital based and occupational screening study, Lee and Costello (1982) observed that Fecatest detected 6 cancers and 4 polyps whilst Haemoccult was positive in only 3 individuals with cancer and 3 with a polyp. The authors claim that Fecatest is more sensitive than Haemoccult in this study (5.5% v 2% positivity) yet does not produce unmanageably high numbers of false positive cases. However, the predictive yield for a positive Fecatest is 14% for neoplasia compared to 26.9% for Haemoccult.

Although Lee (1983) has felt that Fecatest can be used cost effectively for population screening, Berretta et al (1978) have shown that the positivity for Fecatest in 150 unselected patients was 50% and that in their opinion Fecatest most certainly was not suitable as a screening agent.

Controlled Screening Studies with Haemoccult

Despite the multitude of screening studies only 4 controlled studies are in progress (Gilbertsen et al, 1977; 1980; Winawer et al, 1977, 1980; Hardcastle et al, 1983; Kewenter et al, 1984). Whilst these studies are as yet incomplete and therefore the impact on survival and mortality of FOB testing not known some lessons have been learned from interim reports.

Hardcastle et al (1983) have established a controlled study of 20,525 patients taken from general practitioners lists and offered half the opportunity of repeated FOB screening with Haemoccult. Their reported findings include a FOB positivity rate of 2.1%, a 50% predictive yield for neoplasia with 9 of 12 cancers being Dukes' Stage A lesions, and an overall compliance rate of

36.8%. In the control group 10 cancers (4 Dukes B, 4 Dukes C and 2 Dukes D) were detected at one year i.e. one per 1000 controls compared to 3.6 per 1000 in the screened group. In a further 27 FOB +ve subjects 40 polyps were detected. Fibreoptic sigmoidoscopy detected 10 of 12 cancers within its range and 39 adenomas. Double contrast radiology identified only 9 of the 12 cancers and 24 (62%) of the polyps. Colonoscopy was performed in all cases thus allowing comparison with radiology.

In their latest report Hardcastle et al (1985) have found 4 further cancers on rescreening with Haemoccult and one cancer has come to light having been missed by FOB testing. In the control group in the second year of follow-up a further 7 cancers have presented (4 Dukes' B and 3 Dukes' C).

Kerwenter et al (1984) have initiated a controlled study of 21,700 individuals aged 60-64 years in Gothenberg using Hemoccult II. They have compared rehydration with non-rehydration in this study also.

In the non-rehydration group they found 1.9% positive FOB's and on investigation 4 cancers and 19 patients with polyps (predictive yield 27%). However, over the following 18 months 14 patients have presented with colorectal cancer giving an 'at best' sensitivity for non-rehydrated Hemoccult II as 22%. For the rehydration group 5.8% had a positive FOB, 12 patients were found to have cancer and 37 to have adenomas upon examination (predictive yield 18.4%). No subjects in the second group have presented with cancer subsequently. In the control group of 13,700 subjects, colorectal cancer was diagnosed in 12 individuals

(0.88 per 1000). The Dukes' staging for all three groups, however, was not shown to be different. This group stressed the value of rehydration of Hemoccult II and only with rehydration would screening with Hemoccult II become viable.

From the American centres it has become clear that flexible sigmoidoscopy is superior to rigid sigmoidoscopy even in the range of the rigid instrument (Winawer et al, 1980), that 44% of cancers detected on FOB testing are beyond the range of the flexible sigmoidoscopy (Nivathongs et al, 1983) and that colonoscopy is superior to double contrast barium studies for the detection of colorectal neoplasia (Gilbertsen et al, 1980; Winawer et al, 1980). Further that by using flexible sigmoidoscopy routinely in all patients, Winawer et al (1980) have shown a false negativity for polyps on FOB testing to be as great as 76% when present in the recto-sigmoid region.

Tumour Markers

In this thesis only four of the many possible substances that have been investigated as potential biochemical markers of cancer have been assessed; they are carcinoembryonic antigen (CEA), alpha-1-acid glycoprotein (AGP), C-reactive protein (CRP), and gamma glutamyl transpeptidase (GGT).

Berlin (1981) has proposed that the successful cancer diagnostic test is one which will detect 75% of all cancers when 90% of these cancers have not metastasised. The test should also indicate the organ where the cancer resides since this information is essential if curative treatment is to be instituted. Unfortunately, no such marker exists as will be highlighted by the

review of the best known agent CEA. However recent developments in the preoperative asssessment of cancer of the large bowel and the stomach have precipitated the re-examination of the value of the combination of these four tumour markers to predict the presence of cancer in a symptomatic patient.

Carcinoembryonic Antigen (CEA)-Biochemical Review

Carcinoembryonic antigen (CEA) was discovered in 1965 and defined as a tumour-specific antigen of the digestive system (Gold and Freedman, 1965). The fact that CEA was absent from corresponding normal adult tissues, but was present in human embryonic digestive organs by the immunological techniques employed in the initial observations, accounts for the designation given the molecule. It has been proposed that the reinitiation of its synthesis by bowel cancer cells in the adult is the result of a process variously known as derepressive dedifferentiation, retrodifferentiation or antigenic reversion.

The CEA molecule was characterized as a glycoprotein with a molecular weight of approximately 200,000 daltons, sedimentation coefficient of 7-8s and possessing negative electrophoretic mobility (Gold 1967; Gold et al, 1968; Krupey et al, 1967, 1972; Coligan et al, 1972; Newman et al, 1974; Banjo et al, 1974), and possesses 50-60% carbohydrate (Banjo et al, 1972,74; Terry et al, 1972, 1974; Coligan et al, 1975; Slayter and Coligan, 1976). Electronmicroscopy studies reveal that CEA consists of twisted rod-shaped particles, measuring 9 x 40 nm (Slayter and Coligan, 1975; Egan et al, 1976).

Studies with immunofluorescence (Gold et al, 1968; Von

Kleist et al, 1969; Burtin et al, 1972; Denk et al, 1972, 1973; Burtin et al, 1973; O'Brien et al, 1979; Potomski et al, 1979; Pihl et al, 1980) and electron microscopy (Gold et al, 1970; Huitric, 1973; Heberman et al, 1975) in tissue sections of adenocarcinomas of the digestive system, revealed that CEA is situated to a large extent in the glycocalyx on the luminal surface of the membranes and in the cytoplasm. These findings lead to the conclusion that CEA is a secretion product (Denk et al, 1972; Rogalsky, 1975) rather than a cell constituent (Gold et al, 1970). From this site CEA can be released into the circulation of the cancer-bearing host. This has enabled the development of radioimmunoassays to detect the presence of the molecule in blood (Thomson et al,1969; Hansen et al,1974) and has resulted in a proliferation of reported studies on the levels of CEA in the clinical setting.

CARCINOEMBRYONIC ANTIGEN (CEA) - CLINICAL REVIEW

CEA levels in colorectal neoplastic and premalignant conditions.

Thomson et al (1969) described a radioimmunoassay for CEA in serum. Thirty-five out of 36 patients (97%) who were known to have cancer of the large bowel, presented with raised levels in their sera but the antigen could not be demonstrated in patients with cancerous and non-cancerous conditions of the non-digestive organs nor in benign gastrointestinal disorders. This high positivity of CEA for colorectal cancer was subsequently confirmed in other publications ranging from 81% to 95% (Lo Gerfo et al, 1971; Reynoso et al, 1972; Meeker et al, 1973; Gold et al, 1973; Khoo, 1974; Martin et al, 1976; Alsabati and Kamel, 1979). However

several reports have not reproduced these optimistic results and a fall below 70% in the pre-operative CEA positivity rate has been observed (Dhar et al, 1972; Laurence et al, 1972; Mach et al, 1974a; Nugent and Hansen, 1974; Booth et al, 1974a; Onizawa et al, 1976; Mor et al, 1977; Jubert et al, 1978; Slater et al, 1979a; Beatty et al, 1979).

The relationship between CEA levels and histopathological examination of colorectal cancer

1. Staging

The Joint National Cancer Insitute of Canada/American Cancer Society reported that 62% of 147 patients with large bowel cancer had raised CEA pre-operatively; 28% Dukes' A, B1; 58% B2, C1; 83% C2 (Miller et al, 1974). The incidence of a positive CEA has also been observed to vary with the stage of the cancer in other studies ranging from 14 to 44% in patients with Dukes' A, 45 to 76% with Dukes' B and 60 to 100% in individuals with metastatic disease (Dhar et al, 1972; Lo Gerfo et al, 1972; Laurence et al, 1972; Shuster et al, 1974; Livingstone et al, 1974;Booth et al, 1974a; Luporini et al, 1976; Beatty et al, 1979).

2. Vascular invasion

Necrosis and vascular invasion seems also to correlate with CEA level and it was suggested that CEA being a cell surface antigen may be washed off by exposure to the bloodstream (Bivins et al, 1975).

3. Site of primary tumour

Right-sided colon tumours have been described as having a lower incidence of raised CEA than left-sided neoplasms (Shuster

et al, 1974; Livingstone et al, 1974; Martin et al, 1976; Slater et al, 1979). 40% of neoplasms of the caecum show increased CEA levels, with potentially curable lesions (Dukes' A, B and C) being positive in only 33% of the cases. Similarly, CEA in cancer of the rectum was elevated in only 52% of patients, most of them with distant spread, termed Dukes' stage D (Turnbull et al, 1974), and who therefore had a poor prognosis. On the other hand 76% of all sigmoid tumours had positive titres, 73% of these patients having potentially curable lesions. Neoplasms in the right colon were positive in 54%. However the highest positivity was observed in tumours of the splenic flexure to sigmoid colon with an incidence of 77% (Shuster et al, 1974).

Correlation have also been observed between tumour size (Nakamura et al, 1978; Arnaud et al, 1980) and degree of tumour cell differentiation (Sugarbaker, 1976; Martin et al 1976; Arnaud et al, 1980) with the CEA values. The poorer the differentiation of the tumour, the lower is the CEA level. It must be stated however that these strong correlations noted above are not borne out by the following reports: the location of the tumour (Sugarbaker, 1976; Jubert et al, 1978; Miwa et al, 1980; Arnaud et al, 1980); the size of the primary lesion (Shuster et al, 1974; Livingstone et al, 1974); the pathological stage (Bivins et al, 1975; Boyd et al, 1976) and the tumour grade (Imaeda et al, 1976; Boyd et al, 1976; Cooper et al, 1979; Chapuis et al, 1980).

Two proper screening studies and several case finding studies termed "screening" have been reported in the literature. Stevens et al (1975) screened the elderly population of the town

of Busselton, Australia. Their study of 956 unselected persons over the age of 60 years revealed 44 (4.5%) had a CEA level greater than 5 ng/ml at the beginning of the study. During a four year follow-up, 6 of these 44 had died of CEA-associated cancers, 15 were heavy smokers, 2 had colonic diverticula and one a peptic ulcer. By contrast, 18 (2%) of the original 912 CEA negative group had developed CEA associated cancers during the same period. 20 subjects who were CEA positive when re-examined 4 years later, revealed 2 occult cancers, one of the lung and one of the colon. It was concluded that the specificity of the CEA and the high levels in smokers detract from its usefulness as a population screen.

Holyoke et al (1982) performed CEA estimations in a group of 1800 older aged businessmen and two unsuspected cancers were discovered, one in the pancreas, one in the colon: both were incurable. The authors felt this approach was unreasonably expensive for the yield it provided.

Constanza et al (1974) assessed the value of CEA measurements in a population of 205 mixed cancer patients and 553 non-cancer but symptomatic patients. 15 of 23 (65%) colon cancer subjects had raised CEA levels and 9 of 13 early lesions were positive. However, 98 (18%) of the non-cancer group had a raised CEA and of these one developed a carcinoma over 5 year follow up.

El Roubi and Lasne (1978) "screened" 786 subjects for CEA levels. They reported that 37% colorectal cancers were detected with a false positive rate of 33% for the benign GI disease group.

Finally, Klein (1978) performed a comprehensive

investigation of 500 subjects reviewed for proctoscopy, flexible sigmoidoscopy, FOB testing, colonic lavage for CEA and plasma CEA levels, plus barium enema. 7 cancers, 9 villous adenomas and 22 adenomatous polyps were found but the faecal and plasma CEA levels were entirely non-contributory.

CEA and High Risk Groups for Colonic Cancer

(a) Colorectal polyps

Isaacson and Le Vann (1976) have shown CEA to be present in colorectal polyp tissue. The literature gives conflicting evidence as to the levels of circulating CEA in the serum and the value of CEA in this situation. El Roubi and Lasne (1978) reported that 7 of 21 polyps had very high levels of CEA and Ziegenbein et al (1980) noted 52% polyps to have elevated CEA levels which fell on polypectomy to normal. However, Constanza et al (1974) and Miller et al (1974) found the test to be totally insensitive to the presence of colonic polyps.

The risk of patients with colorectal adenomata possessing elevated CEA levels and subsequently developing carcinoma was discussed by Doos et al, (1975). Fourteen of 93 patients had CEA levels greater than 2.5 ng/ml and 7 of them had malignant (2) or pre-malignant (5) changes within one year of follow-up. CEA titres were associated with the increasing age of patients, villous type histologically and cumulative adenoma volume over 6 cm^3. No significant association was observed between the antigen values and dysplastic changes or carcinoma-in-situ.

(b) Inflammatory bowel disease

The presence of augmented concentrations of CEA in

inflammatory bowel disease was first reported by Lo Gerfo et al, in 1971 and further confirmed by Kleinman and Turner (1972) in patients with Crohn's disease. Although variable results have been obtained, it is generally accepted that approximately 10% of these individuals have raised CEA titres which appear related to symptomatic disease (Moore et al, 1972a; Turner et al, 1973; Hansen et al, 1974; Martin et al, 1976). However, Rule et al (1973) reported a higher proportion of positive values with the incidence of an elevated CEA being 36.6% in 30 patients with granulomatous colitis and 27% in 26 patients with ulcerative colitis.

The CEA level has also been associated with the extent (Gardner et al, 1978) and degree of disease activity (Moore et al, 1972a; Wight and Gazet, 1972; Rule et al, 1973; Booth et al, 1974; Hansen et al, 1974; Mitchell et al, 1975; Martin et al, 1976), generally returning to normal levels following remission or total colectomy (Rule et al, 1973). Furthermore persistent elevation has been found in patients with longstanding Crohn's disease (Booth et al, 1974). Dilawari et al (1975) tried to predict the presence of severe dysplasia or cancer in a group of long-standing colitis. The levels of 6 of 7 patients with cancer and 6 of 7 with severe dysplasia were no different from those obtained in a control group of uncomplicated colitis patients.

CEA levels in gastric cancer

The measurement of plasma CEA to indicate gastric cancer suffers from the same drawbacks as for colorectal cancer - low sensitivity particularly for early stage I & II cancers and low

specificity. The following table (1.4) indicates the % sensitivity of CEA by stage for the principal reported series of gastric cancer.

CEA levels seem to depend on the degree of tumour cell differentiation (Chatal et al, 1976; Dedieu et al, 1977), with lower titres present in the more poorly differentiated lesions. The prognostic value of preoperative CEA in stomach cancer patients has not been yet confirmed (Ellis et al, 1978) although a raised value after resection has been associated with residual tumour or metastases (Chatal et al, 1976; Dedieu et al, 1977).

As seen in the above table (Table 1.4), the extremely low levels of CEA in early gastric carcinoma have discouraged the use of plasma CEA levels as a method of screening. However, there has been considerable interest in analysis of gastric juice for CEA and associated CEA-like proteins.

4 groups of workers (Fujimoto et al, 1979; Bunn et al, 1979; Satake et al, 1980 and Tatsuta et al, 1980) have investigated the activity of gastric juice CEA in patients with benign gastric disease and patients with gastric cancer. In these studies elevated gastric CEA levels were found to be consistently more accurate than plasma CEA levels ranging from 54.5-75% elevation - for early gastric cancer and 52-100% for advanced cases (see Table 1.5).

These reports were preliminary studies and supported the potential of gastric juice over plasma CEA to identify early and advanced gastric cancers but the specificity of the test does seem

Table 1.4

Levels of CEA by stage in gastric cancer

Reference	No. patients	Origin	% raised CEA			
			Stage I	II	III	IV
Tomada et al (1978)	226	Japan	8	25	23	40
Ellis et al (1980)	157 inoperable	UK				31
Hine et al (1979)	24	UK	4.5			19.4
Bunn et al (1979)	25	USA	100			20
Fujimoto et al (1979)	39	Japan				32
Staab et al (1980)	375	Germany	18.5		23	23
Satake et al (1981)	92	Japan	0			17
De Mello et al (1983)	100	UK	15		35	52

Table 1.5

Sensitivity and specificity of gastric juice CEA for cancer

Author	Early Gastric Cancer		Adv. Gastric Cancer		Specificity
					%
Bunn et al (1979)	uncertain data		23/25	92%	61
Fujimoto et al (1979)	6/8	75	18/34	100	100
Tatsuta et al (1980)	12/22	54.5	18/34	53%	95
Satake et al (1980)	13/16	81.3	17/19	89.5%	84

to fall in the presence of active peptic disease. The authors have therefore suggested that rather than general screening, surveillance of "at risk" populations e.g. Pernicious Anaemia patients (persistently elevated in the study of Bunn et al, 1979) would be more valid.

True population screening for gastric cancer has been performed using gastric juice analysis. Hakkinnen (1980) has used not CEA but fetal sulphoglycoprotein antigen (FSA) to screen 40,000 individuals in a rural Finnish community. The compliance rate was 75% and a positive rate on testing of 8.8%. Endosopy was performed on nearly all FSA positive subjects (92.5%) and 35 cancers were identified plus one gastric carcinoid, 10 adenomas and 45 peptic ulcers. In only 6 subjects with cancer were symptoms present and subsequent surgical resection showed the stages of the 35 cancers as follows: 19 Stage I; 6 Stage III; 10 Stage IV.

In the United Kingdom gastric juice analyses to detect gastric cancer has been reported using a ratio of lactate dehydrogenase and B-glucoronidase (Rogers et al, 1981). In this study, 113 patients with dyspepsia were investigated fully including gastric juice analysis. By mathematical manipulation an index dependent on the ratio of LDH:B-glucuronidase could identify 41/42 cancers whilst maintaining a specificity of 89%. 2 of 3 early gastric cases were identified in this way. The authors proposed this may be a suitable screening agent for high risk populations such as the coal miners in the high incidence area of South Wales.

No follow up data is available from these authors so one

must conclude that this approach to screening for gastric cancer has fallen from favour.

Non-specificity of the CEA Radioimmunoassay

Despite early support for the concept of CEA being colon cancer specific (Thomson et al,1969; LoGerfo et al,1971) it soon became clear that not only did other digestive and non-digestive tract tumours exhibit elevated levels of CEA but so did patients with benign conditions of the liver, lungs and the gut.

Cross-reactivity of the CEA radioimmmunoassay with other tumours

LoGerfo et al (1971) demonstrated elevated CEA levels, not only in the sera of patients with GI tract cancers but also in tumours affecting lung, breast and prostate. The presence of CEA titres in cancers other than the GI tract has since been widely confirmed (Booth et al,1973; Meeker et al,1973; Hansen et al,1974). Reynoso et al (1972) found an overall CEA positivity in 31% and 28% of patients with cancer of the male and female genito-urinary tract respectively. Abnormal elevations of CEA were also found in patients with lung cancer (70%) and breast cancer (15.7%).

CEA levels in normal subjects and patients with benign conditions

A multi-institutional collaborative study on CEA in 10,000 patients in the United States, Canada and the United Kingdom using the Z-Gel method of Hansen has been performed (Hansen et al, 1974). Titres greater than 2.5 ng/ml (accepted normal level) were observed in 8.3% of healthy individuals, while only 1.6% were above 5 ng/ml. In this group the smoking history appeared to interfere with the CEA titre, since 19% of the smokers had CEA

levels above the normal range, while only 3% of non-smokers had elevated levels. In those patients with benign disorders 34% had levels of 2.6% or greater with the highest positive titres observed in those patients with alcoholic cirrhosis, pulmonary emphysema, pancreatitis, kidney transplant, granulomatous colitis and alcohol addiction. The high false positive rate could be reduced to 7.6% by considering titres above 5 ng/ml at the expense of increasing the proportion of false negative results to 52.5% in the group of patients with cancer (Hansen et al, 1974).

CEA has since been noted to be elevated in a considerable number of benign conditions ranging from peptic ulceration, pancreatitis, diverticulitis to benign liver diseases (Beatty et al, 1979; Hansen et al, 1974; Miller et al, 1974; Moore et al, 1971, 1972b).

National Institute of Health consensus statement on CEA

The extensive investigations of the role of CEA as a single agent in the management of gastrointestinal cancer has revealed that this marker is insensitive, has a low specificity and cross-reacts with other tumours. In the consensus view of the NIH (1981) CEA is not suitable for screening an asymptomatic group, is unreliable in the detection of symptomatic cancer and has limited value in the monitoring of the postoperative patient.

Current use of CEA

CEA has been used in the postoperative surveillance of cancer patients, and the response to chemotherapy (Steele et al, 1980). New emphasis is now being placed on the potential for immunoscintigraphy to detect tumours secreting CEA and also for

targeting chemotherapeutic agents bound to anti-CEA monoclonal antibodies at tumour deposits (Britten and Granowska, 1985).

Combination of carcinoembryonic antigen with other tumour markers: its role in the clinical diagnosis and assessment of patients with digestive tract cancer

The measurement of different tumour-related substances in conjunction with the CEA assay has been attempted in order to improve the detection rate of gastrointestinal cancer. The simultaneous assay of plasma CEA and serum enzymes such as gamma glutamyl transpeptidase (GGT), (Steele et al, 1974); Munjal et al, 1976a; Miron et al, 1979) or phosphohexose isomerase (PHI), (Munjal et al, 1976a-78) may be useful in the differentiation between hepatomegaly due to metastatic cancer and benign hepatic disorders. Furthermore, serial concomitant estimations of these "markers" might predict liver recurrence weeks before clinical confirmation (Cooper et al, 1975; 1976a; Cooper 1978a; Munjal et al 1976a; Neville et al, 1978).

Ward et al (1977) applied a discriminant function for 70 preoperative patients with cancer of the colon with CEA and acute phase reactant proteins (APRP's) measurements to predict those patients who would develop metastases after 'curative' resection. The combination proved significantly better as a prognostic indicator than when using CEA levels alone. Rashid et al (1982) similarly found that a combination of CEA + APRP's could identify those patients with irresectible lesions and whose survival was limited to a mean of 5 weeks. The differences in survival when

both CEA and an APRP were raised were significantly lower $p < 0.002$ than when one or other marker was raised. The value of this preoperative prognostic information is not clear other than perhaps for future stratification of chemotherapy trials or avoidance of surgery when palliation is not needed for symptoms.

The most interesting use of combinations of CEA and other markers is in the preoperative diagnosis of gastrointestinal malignancy with 3 groups of workers reporting stimulating findings. Chu et al (1982) evaluated 72 subjects with colorectal cancer preoperatively. Using CEA alone only 28.6% of Dukes' A,B and C cases were identified, whilst AGP identified 43% corresponding stages. Overall CEA detected 58% cancers with a 79% specificity and AGP detected 57% cancers with an 81% specificity. The combination of CEA + AGP increased the sensitivity for cancer to 79% ($p < 0.01$) whilst the specificity became 67% ($p > 0.10$). Further the detection of the Dukes' A, B & C cases rose from 29-57% ($p < 0.046$). Walker and Gray (1983) reported similar findings for the combination of CEA and the acute phase reactant, serum protein hexase. In this study, CEA alone detected 29% Dukes' B patients and 32% Dukes' C patients (28% overall). Protein hexose was elevated in 71% Dukes B cases and 91% Dukes C cases (75% overall). The addition of CEA and the APRP increased the overall sensitivity to 79% (2 additional Dukes' B identified). Unfortunately the authors have failed to indicate whether there was any significant alteration in the specificity of the combination of tumour markers for the 33 control subjects.

Finally, de Mello et al (1983) investigated the value of a

battery of 6 non-specific tumour markers to determine the preoperative diagnosis of cancer in 200 patients with gastric or colorectal cancer. Using multivariate analysis the group was able to predict 84% patients with cancer with only a 16% false positive rate for the 73 controls studied. Furthermore the group identified 85% Dukes' A & B colorectal lesions and 63% Stage I & II gastric lesions.

From these three studies, there appears to be a pattern emerging that the combination of 2 or more non-specific markers will not only increase the identification of advanced cancers but also will significantly increase the detection of early 'curable' colorectal and gastric cancers. Furthermore, in these small studies where recorded the increase in sensitivity does not apparently lead to an undesirable fall in specificity.

It was these reports which raised the question of whether a re-evaluation of the value of tumour markers in the detection of early gastrointestinal cancer was feasible when used in combination since one would rarely diagnose cancer on the basis of a single symptom.

Acute Phase Reactant Proteins (APRP's)

General Aspects

There are a great many proteins which fall into this group e.g. caeruloplasmin, haptoglobin, fibrinogen and serum Amyloid A but the commonest proteins investigated in relation to human malignancies are alpha-1-acid glycoprotein (AGP) C-reactive protein (CRP) and alpha-1-antithymotrypsin (ACT). Only AGP and CRP will be discussed further.

C-reactive protein comprises five identical covalent bound units each of approximately 21,000 daltons molecular weight and they join to form a pentagonal shape (Kushner et al, 1981). Alpha-1-acid glycoprotein has a molecular weight of approximately 40,000 daltons, containing 45% carbohydrate in the moiety (Schmidt, 1975). AGP does exhibit some microheterogeneity especially related to glycosylation (Wells et al, 1981) and thus appears to be influenced by endogenous oestrogens. CRP is a pure peptide and is not altered by hormones.

The biological function of these proteins is not clear but they derive this name of acute phase reactant proteins as part of the host's response to injury. In addition to the containment and removal of the injurious agent, removal of any damaged tissue and repair and restoration of function, the inflammatory response stimulates an increase in the hepatic synthesis of proteins - the acute phase reactants. Koj (1974) suggests that a humoral factor is responsible for eliciting the acute phase phenomena through the continuance of tissue necrosis and inflammation. Raised levels of these proteins are therefore found in a multitude of illnesses including cancer and are therefore a reflection of a non-specific response to "injury".

Both CRP and AGP have been found in tissues in relation to acute inflammatory change in arthritis and myocardial infarction (Kushner et al, 1963; Kushner et al, 1980). Conflicting reports appear in the literature as to whether APRP's can be localised to tumour tissues. Twining and Brecher (1977) identified AGP in breast, colon and stomach cancers; however Uete et al (1970) were

unable to localise CRP in gastric cancer tissue.

During tissue destruction, CRP and AGP may remain elevated and at levels corresponding to the severity of tissue damage (Fisher and Gill, 1975). Experiments in vitro have shown that CRP (Mortensen et al, 1975, 1976) and AGP (Chiu et al, 1977) may inhibit some immunological responses, such as lymphoblastogenesis and mixed lymphocyte reactions. The suppressive effect was predominantly directed upon T-cell mediated functions. Furthermore, Kushner et al (1981) have shown that CRP will activate complement and initiate phagocytosis by macrophages.

APRP's and cancer

Shetlar et al (1955) have proposed that raised circulating levels of glycoproteins occur in carcinomata as a result of cellular proliferation and inflammation. Cooper and Stone (1979) reported that a continuous rise in APRP's was associated with a rapid course of a tumour and similarly Rashid et al (1982) have reported a sudden and maintained elevation of APRP's immediately prior to death.

Since the APRP's are a non-specific marker for tissue injury they have not been used as a screening study to elicit cancer. However, they have been shown to be present to high levels in advanced tumours (Ward et al, 1977; Kelly et al, 1978).

Recent reports are available in the literature concerning the sensitivity of AGP and CRP in the detection of colorectal and gastric carcinomata. Walker et al (1981) examined 104 patients with a preoperative diagnosis of colorectal cancer and found 78 (75%) to have elevated AGP levels compared to only 33% with raised

CEA levels. Cooper and O'Quigley (1982) noted that 45% Dukes' A + B, 67% Dukes' C and 84.6% Dukes' D patients had raised APRP's whilst Raynes and Cooper 1983 reported only 24.3% Dukes' A+B had raised CRP, 47% Dukes' C and 90% Dukes' D patients were found to have elevated preoperative CRP levels in this study.

When they investigated 75 gastric cancer subjects, Raynes and Cooper (1983) found that 8/50 patients with stage I-III had an elevated CRP but 24 (96%) with advanced gastric cancer had CRP level > 10 mg/l. Grindulis et al, (1981) reported 12/17 gastric cancers had elevated CRP levels (70%) but that 22/52 subjects with benign inflammatory conditions of the stomach also had elevated CRP levels which were statistically indistinguishable from the cancer range. This precluded their routine investigation in the opinion of the authors as the overall specificity of the CRP was 75%.

Finally, in parallel with studies of gastric juice for CEA levels, Rapp et al (1972) measured AGP levels in gastric juice and found an elevation in 89% of 34 individuals with gastric cancer and only in 12% with peptic disorders.

In summary, the APRP's are even less specific than CEA and as with that marker elevated levels when present in cancer tend to be associated with advanced disease.

Gamma-Glutamyl Transpeptidase

Gamma-glutamyl transpeptidase (EC 2.3.2.2) is a membrane bound glycoprotein which catalyses the transfer of gamma-glutamyl groups between peptides or amino acids (Rosalki 1975; Tate and Rose 1977). The physiological function of GGT is thought to

involve the mediation of amino acid translocation across cell membranes (Griffiths et al, 1979). Although the highest concentration of GGT is found in the brush border lining the luminal surface of the cells of the proximal convoluted tubules of the kidney, the enzyme has been demonstrated in a variety of other human tissues and body fluids (Rosalki, 1975).

The major role of the enzyme is as an indicator of hepatobiliary dysfunction and has been used to screen for alcohol abuse (Rosalki and Ray 1972; Rolleson et al, 1972). However, in a major review of the clinical value of GGT as an indicator of hepatobiliary disease of benign origin, Penn and Worthington (1983) have seriously questioned the need for the test to be performed in a clinical laboratory in preference to the standard liver function tests.

In the diagnosis of gastrointestinal cancer an elevated GGT is taken to indicate the possible presence of hepatic metastases. Preliminary studies revealed that approximately 90% of anicteric patients with liver replacement by tumour presented with abnormal levels in their blood (Rutenburg et al, 1963; Kokot et al, 1965; Aronsen et al, 1970). However, further reports have not confirmed these initial findings and a fall in the sensitivity of the assay was noted with a significant increase in the number of false positive results (Baden et al, 1971; Irvin et al, 1973; Almersjo et al, 1976; Beck et al, 1979). Furthermore, its measurement was not superior in this context to conventional liver function tests (Baden et al, 1971; Irvin et al, 1973). Moreover, transient elevations have been observed in the immediate

postoperative period after curative resection of colorectal carcinoma (Steele et al, 1974; Beck et al, 1979).

Thus in isolation, gamma-glutamyl transpeptidase has little in the way of sensitivity or specificity to indicate liver dysfunction secondary to metastases. However, in the following section the interaction of GGT and other "tumour markers" can indicate a role for GGT in cancer patients.

Questionnaire

General

The use of questionnaires is now commonplace in medical research. The range of practice is broad, varying from defining risk of heart disease in civil servants (Rose et al, 1977) adjuncts to medical history taking (Brodman et al, 1951; Pecaroro et al, 1979; Gumpel and Mason, 1974) to highly sophisticated psychology research (Becker 1976). It is not surprising, therefore, that there should be interest in the use of questionnaires to screen for colorectal neoplasia (Silman et al, 1983; Farrands and Hardcastle, 1984) or to predict risk of gastric disease, including gastric cancer, on the basis of a questionnaire response (Mann et al 1983).

The value of self-administered questionnaires used for whichever purpose, is that they are generally quick to complete, cheap to use and readily acceptable to the population. Providing that the basic principles of questionnaire design are followed (Oppenheim, 1978; Pecaroro et al, 1979) the data so collected will also be reproducible, consistent and not subject to the bias that can occur from visual and voice clues given in an informal

interview (Collen et al, 1969).

Questionnaire and Colorectal Cancer Screening

Schewe et al (1979) suggested that a symptom questionnaire may identify those individuals with cancer of the large bowel who were FOB negative. Whilst this was based on a hospital population it was felt that there may be some value for symptoms as markers of colonic cancer in general screening.

Until recently, there has been little evidence to support symptom screening for colorectal neoplasia. Most studies of symptomatic cancer patients have shown that there is no relationship between length of symptoms and stage of cancer at diagnosis. Whilst Keddie and Hargreaves (1968), Irwin & Greaney (1977) and Holliday and Hardcastle (1979) showed no correlation at all between duration of symptoms and stage McDermott et al (1981) have shown that the longer the symptoms were present the better was the prognosis. Further Welch and Donaldson (1974) reported their experience at the Massachusetts General Hospital, Boston where they reduced the delay in patient presentation from 7 months to 2 months before treatment but found no alteration in the number of localised and advanced lesions at laparotomy.

Another fundamental obstacle to the use of a questionnaire to screen for colorectal neoplasia is the prevalence of symptoms normally taken to indicate significant pathology of the colon and rectum within the population at large. Thus Thomson and Heaton (1980) in a study of 301 apparently healthy individuals found that 62 regularly experienced abdominal pain and in 41 of these the pain was relieved by defaecation. 31 further individuals were

regularly constipated and 14 experienced episodic diarrhoea. Jones (1976) also noted 36 of 112 normal adults had rectal bleeding at some time and 72% were prone to episodic diarrhoea. Thus any questionnaire to detect just such symptoms at a given moment in time might select a large proportion of the general public for further investigation.

Similarly, the symptoms of large bowel dysfunction may well be secondary to benign pathology and not just malignancy. Tada et al (1978) used a questionnaire in 304 patients, who were a mixture of referred and screening individuals and found that the analysis of symptoms could not distinguish early colon cancer or colonic polyps from normal individuals who showed similar symptom distributions. Clamp and Wenham (1984) have shown that in "symptomatic" individuals the use of a structured questionnaire, whose data can be analysed by mirocomputer, can accurately predict the presence of colorectal cancer (83%) and that this prediction would be enhanced by the use of FOB testing (93% sensitivity).

Despite the theoretical and practical considerations above, two groups of workers have explored the value of self-completed symptom questionnaires as part of a colorectal neoplasia screening study (Silman et al 1983; Farrands and Hardcastle 1984).

Silman and his colleagues investigated 1195 individuals aged over 40 years from a working population. A 9 item questionnaire to elicit bowel symptoms was used in conjunction with FOB testing to screen for colorectal neoplasia. 28 (3.1%) individuals were Haemoccult positive and 114 (12.4%) had one or more symptoms. All positives (129 persons) were examined by

flexible sigmoidoscopy and barium enema. No cancer was found but 7 subjects with adenomas greater than 1 cm were discovered. Each of the 7 patients reported at least one symptom (dark red bleeding in 4, bright red bleeding in 2 and diarrhoea in 1) and 6 were Haemoccult positive. There was no individual with a Haemoccult positive adenoma without symptoms. Predictive values for these adenomas for Haemoccult positive tests (21%) self-reported dark bleeding (16%) and diarrhoea (17%) were significantly higher than for other symptoms. As with Clamp and Wenham (1984) it was found that the predictive value rose significantly to 46% for Haemoccult positive individuals who had at least one symptom ($p < 0.05$) and to 57% when a positive FOB was associated with dark red bleeding.

Silman and his colleagues drew up three conclusions regarding their study: (a) FOB testing may not be identifying "asymptomatic" patients as often as had been previously thought; (b) the addition of self-reported large bowel symptoms improves the performance of Haemoccult as a screening test and (c) the presence of dark red bleeding, which can be ascertained using a symptom questionaire, has a predictive value for adenomas over 1 cm, comparable with Haemoccult and thus may have a separate role in screening.

By contrast Farrands and Hardcastle (1984) concluded that self-reported symptom questionnaires were of little value in the early detection of colorectal neoplasia. In their study, using a very simple 5 item questionnaire plus FOB's to screen, 527 questionnaires and 483 FOB's were available for analysis. Colonoscopy revealed 6 of the 12 individuals positive for one or

more Haemoccult slide had significant colorectal neoplasia (2 cancers; 4 polyps). This represents a predictive yield of 50%. The responses to the questionnaire revealed 128 (24.4%) had one or more positive symptoms. On full investigation of these individuals only one was found to harbour any neoplastic lesion, revealing an 85% false negative rate and a positive predictive yield of 0.78%. The authors' conclusions were that symptom questionnaires were of little value in colorectal cancer screening compared to FOB testing.

Questionnaires and Gastric cancer

Early gastric cancer (EGC) has been reported by several workers to be symptomatic (Table 1.6) and that these symptoms may be present for many months prior to diagnosis (Fielding et al 1980; Green et al 1981; Correia et al 1981; Rosch 1981).

The commonest symptom is that of upper abdominal pain or discomfort ranging from 28.9% cases in the Birmingham study (Fielding et al 1980) to 92% in the Portugese study (Correia et al, 1981), whilst an unexpectedly high incidence of gastrointestinal haemorrhage 24-32% was noted by Rosch (1981), Green et al (1981) and Correia et al (1981).

The duration of symptoms in these patients with EGC ranged widely between the studies. The Birmingham study (Fielding et al 1980) revealed that only 15.6% patients had experienced symptoms for more than one year, whilst Green and his colleagues (1981) noted that the mean duration of symptoms for EGC was 36 months compared to 6 months for advanced cancer. Correia et al (1981) found that 50% patients had experienced symptoms related to EGC for 5 years or more whilst only 23% had had symptoms for less than 12 months.

Table 1.6

Incidence (%) of symptoms in Early Gastric Cancer

	Abdo Pain	Weight loss	Vomiting	GI haemorrhage
Fielding et al (1980)	28.9	18.9	23.3	6.6
Green et al (1981)	82	'low'	-	32.1
Correia et al (1981)	92	62.5	68.4	31.6
Rosch (1981)	74	41	32	24

These features would suggest that there may be a potential role for a symptom questionnaire to screen for EGC. Unfortunately there are a great many factors that have conspired against previous attempts to identify cancer or peptic ulcer on the basis of symptoms.

One such factor is the prevalence of symptoms within the population at large. Whilst the true prevalence of "dyspeptic" symptoms within the population is unknown, audit of GP referral patterns have shown that 1% of all visits to the GP relate to upper GI, "dyspeptic" symptoms (Gear and Barnes, 1980). A postal survey of a North East Scotland practice revealed 29% had experienced symptoms suggestive of peptic ulceration at some time (Weir et al, 1967).

If we consider the incidence of symptoms commonly seen in EGC with that found in patients presenting with benign disease it is also difficult to discriminate between the two. Horrocks et al (1978) reported an analysis of 360 patients carefully assessed and followed through surgery. The incidence of upper GI pain was clearly high in both groups with little to distinguish between cancer pain (except the degree of periodicity) from duodenal or gastric ulcer pain. Similarly, it was noted that weight loss of more than 4 kg in the weeks preceding diagnosis was noted in 85% of patients subsequently found to harbour gastric cancer, but also a similar degree of weight loss was found in patients with gastric ulcer (62%), duodenal ulcer (44%), non-ulcer dyspepsia (32%) and finally in cholecystitis (23%). This group concluded that the

symptoms of gastric cancer were vague and difficult to distinguish from those of other gastroduodenal diseases.

Thus in clinical practice if an audit is performed of those patients investigated by either barium meal examination or upper gastrointestinal endoscopy, it is not uncommon to find that only 20% of those examined will exhibit pathological abnormalities (Table 1.7). The principal diagnoses as shown in the table are duodenal ulcer, gastric ulcer, with gastric cancer accounting for only 1% of all cases except in highly select studies.

Read et al (1982) reviewed 1286 cases investigated for 'dyspeptic' symptoms in the literature and found that only 1.4% cases revealed a gastric malignancy.

It is little wonder therefore that many workers have felt that symptom analysis has little in the way of predictive value when considering the aetiology of upper gastrointestinal symptoms (Mead et al 1977, Horrocks et al, 1978; Marton et al, 1980; Ross and Dutton 1972; Scheinok and Rinaldo 1967, Editorial BMJ 1978, and Mollman et al, 1975). However a recent report from Mann et al (1983) has again raised the possible value of symptom analysis to determine risk of an individual's symptoms representing 'significant' gastroduodenal disease and therefore determining priority for investigation.

In this study, a multivariate analysis of the symptoms elicited by a questionnaire of 235 individuals referred for upper gastrointestinal endoscopy was performed. The analysis was designed to identify those patients with either peptic ulcer gastric cancer or peptic stricture and a predictive equation of

Table 1.7

Principal diagnoses on investigation of 'dyspepsia'

Authors (year)	No patients	Selection	Investigation	% patients with specific diseases D.U.	G.U.	Gastric Ca
Rinaldo 1963	300	GI clinic	Ba	2.3	12	5.3
Ross 1972	1046	2 referral	Ba	17.2	2.5	0.9
Barnes 1974	346	GP	G	12.1	6.4	1.8
Mollman 1975	197	2 referral	Ba + G	25	13	1
Mead 1977	100	GP	Ba	8	2	0
Fisher 1977	304	GP	G	13.5	6.9	1
Horrocks 1978	360	Surgical clinic	G	22.2	13.9	22.2
Marton 1978	495	2 referral	Ba	7	5	0

Ba = barium meal G = gastroscopy

the 6 discriminatory factors was found. This equation was then applied prospectively to 356 patients similarly referred for endoscopy. The system was able to accurately identify 587 patients with the above three conditions whilst reducing the number of investigations (in theory by 30%). In the study, all 52 cancers were recognised by the scoring index devised.

The application of this multivariate approach to the analysis of gastrointestinal symptoms seemed an appropriate pathway to follow in the search for a simple and cheap screening filter for gastric cancer, with implications also for colorectal screening.

What factors affect compliance?

General Review

Compliance is defined as "Action in accordance with a request or command" (Oxford English Dictionary, 1979) and compliance for medical advice or treatment is low generally (Eraker et al, 1984). Compliance for screening tests is a critical factor in the potential cost effectiveness of such programmes and as such is worthy of considerable attention, yet few factors are appreciated which will influence response or non-response to screening opportunities. The largest experience in screening for cancer is in cervical and breast cancer where compliance rates range from 5%-65% for breast cancer (Chamberlain, 1975; Shapiro, 1978) and 17%-95% for cervical cancer (Sansom, 1972; Cardiff Cervical Cytology Study, 1980).

Certain general factors which influence response to screening have been elicited from screening for cervical and

breast cancer. Age and social class are factors one would consider as being important determinates of screening activity. Wakefield and Sansom (1966) have shown that increasing age and lower social class were associated with low compliance for cervical cancer. Similarly, the Cardiff Cervical Cytology Study (1980) found the largest compliance group to be aged 25-29 years were also members of social class I (95% compliance), compared with the lowest compliance group social class V (20%), who were older than 60 years.

It has also been shown that the method of promotion and the person promoting screening influences compliance for breast and cervical cancer. Thus when a general practitioner extends a written invitation to attend a screening clinic for breast cancer, the response ranges from 57% (Hobbs et al, 1980) to 82% (Edinburgh Breast Screening Clinic, 1978) and compares favourably with the open access approach to a clinic experienced by Chamberlain et al 1975. Cullum and Savory (1983) have investigated the question of who should perform cervical screening and found that the practice nurse or midwife is likely to be most successful in screening young women than the GP or Family Planning Clinics.

Factors Affecting Compliance in Colorectal Cancer Screening with Faecal Occult Blood Testing

Several factors affect compliance for screening for all cancers including age, sex and social class. However, the method of promotion of faecal occult blood testing appears also to be important. These factors will now be reviewed.

Age, Sex and Social Class

Hardcastle et al (1983), Farrands et al (1981) and Million et al (1982) have all reported a falling compliance rate with increasing age. In these three studies compliance for individuals over 70 years was between 17%-27%, whilst in those subjects aged 65 years or less, the range of compliance was 30%-40%.

Hardcastle et al (1983) also revealed a significant difference in compliance between the sexes where 1940 (38.4%) women complied with FOB testing, compared to 1673 (35.1%) men.

Both Farrands et al (1981) and Million et al (1982) suggest that social class affects compliance and that the low compliance they experienced in their studies, 27% and 32.4% respectively, was due to the preponderance of lower social class members in their studies, compared to that of Hardcastle et al (1980) where the return of completed FOB's was 45%. However, social class is not necessarily the sole determinant of screening for colorectal cancer using FOB's, since Dent et al (1980) have shown that in a study of over 300 hospital workers it was the "blue collar" workers and not the doctors or nurses who were more likely to comply.

Promotion of Faecal Occult Blood Testing for Colorectal Cancer Screening

When the FOB test was introduced as part of a regular health check-up facility, it was found to be accepted by the motivated group of volunteers. For example, Fruhmorgen and Demling (1978) found that 83.5% of 6,007 individuals attending the Erlangen clinic completed the FOB test when first introduced. In

the United States, Winawer et al (1977) reported that in addition to sigmoidoscopic examination, 85% of 6597 individuals accepted FOB as part of their screening routine. Furthermore, Gilbertsen et al (1980) have reported that 85% of 48,000 individuals attending the University of Minnesota Medical Centre accepted the addition of FOB's to their usual examination.

When the FOB test is introduced de novo to an unselected population, then a markedly lowered compliance rate can be expected (Table 1.8). In the United Kingdom, where 3 studies have employed postal delivery of the FOB test, the return rates of completed FOB were 27%, 36.9% and 45% (Farrands et al 1981; Hardcastle et al 1983; Hardcastle et al, 1980). In further studies, following a letter of invitation to screen from the GP, those willing to participate either collected the FOB personally from the GP surgery (Lallemand et al, 1984) or contacted the GP and were visited and counselled by a State Registered Nurse (Million et al, 1982). In these studies the response rates were 42% (after 2nd letter, Lallemand et al 1984) and 32.4% (Million et al, 1982).

In all these studies, personalized letters from the subject's own GP, were sent as experience in breast cancer screening had suggested this to be the most favourable input (Hobbs et al, 1980; Edinburgh Breast Screening Clinic 1978).

Similar experiences have been reported in West Germany and the United States where Durst, Newmann and Schmidt (1976) found only 28% persons accepted screening and Helfrick Petrucci and Webb (1979) found only 20% FOB return in a population screening

Table 1.8

UK Screening Experience

Author	Promotion	Compliance (%)
Hardcastle 1980	Postal	45
Farrands 1981	Postal	29
Millions 1982	Postal and District Nurse	33
Hardcastle 1983	Postal	37
Lallemand 1984	Postal (Collect from GP Practice)	42
Lee 1983	Occupational	42
Silman 1983	Occupational	50

programme in Washington DC.

These unacceptably low levels of compliance have led to an exploration of alternative approaches to the public for the promotion of FOB testing. Elwood, Erikson and Liebermann (1978) examined 5 methods of promotion varying in the extent of personal or impersonal contact. In this study, 11,115 members of the American Association of Retired Persons were either sent a letter of explanation and asked to reply if they wished to complete an FOB test to complete, or they were simply sent the FOB pack direct. The third approach was to attend a hospital clinic and the fourth and fifth approaches were either as a part of a group meeting or a direct consultation at home. The response rates were from 8.6% for the clinic attendance approach, 13.6% for those writing to request an FOB, 15.4% completed the test when sent direct, 28.7% responded to the group meeting and 20.4% to the home visit.

Hoogewerf et al (1981) have further investigated the value of the home visit. Their study comprised 152 patients and those who failed to return an FOB within a week were visited at home by a district nurse up to 3 times per individual. Compliance rose to 74%, but clearly is not practicable in mass population screening. Further support for the role of personal contact, as a means for promotiig FOB testing, is found in Hardcastle et al's study (1983) where prior interview during which colorectal cancer and the test were discussed, raised compliance to 51.6% compared to an overall 36.9% ($P < 0.0001$). Hastings (1974) found increased compliance for FOB's following rectal examination.

Several workers have evaluated the workplace as a site for the promotion of the FOB test. Silman et al (1983) approached two large industrial organisations to perform FOB testing on their employees. 1806 employers were approached by letter inviting them to participate. 1195 responded and were sent FOB tests. A follow-up letter was sent if an FOB was not returned complete. During the promotion period lectures, leaflets and group discussions were arranged for the employees. 916 subjects (50.7%) returned a completed FOB.

Lee (1983), similarly, performed screening in 2 factory based populations. In one factory, where the workforce was used to an annual physical examination, 45% (989) men completed the FOB test, whereas in those who received the invitation to screen in their pay packet and who did not receive annual physical examinations, only 22% (1431) men participated.

Miller and Knight (1977) had a 94% return in their study, offering FOB's to military personnel at the Mather Air Force Base. Unfortunately, the true compliance for the study is not known since there was extensive publicity aimed at both active and retired personnel. However, it would seem that the armed forces are used to physical examination and subject to certain discipline which would explain the high return rate seen.

One obvious approach for the promotion of mass screening with FOB testing is the use of the media. In the United States, 3 large studies have been performed utilising extensive TV and newspaper coverage. Whilst Richardson (1977) and Bralow and Kopel (1979) experienced high compliance rates (85% and 79%

respectively), Winchester et al (1980) in Chicago, despite 5 promotions on the TV news, radio and newspaper coverage despatched 54,101 FOB's and received only 14,074 (26%) completed FOB's. Similarly, in the "Frome experiment" Farrands et al (1981) found in the UK despite extensive advertising, the response rate for FOB testing was only 27%.

Compliance for Gastric Cancer Screening

The main thrust of gastric cancer screening is in Japan. Unfortunately, there is no fixed policy for screening which varies from self-presentation to a clinic to attending a mobile screening clinic which attends the workplace. Also patients who are symptomatic and who may also be referred by their GP's are included in the data. The information that is published in the English literature is therefore confusing and limited in volume.

Hirayama (1978) shows that screening however does vary by age and sex. In 1975, of the total adult population of Japan, 3.4% males and 2.3% females were screened. The peak age for screening was 45-55 years, where 7.5% men and 5.4% women underwent screening. However, selection bias may be strong since a great deal of screening appears to be aimed at factory workers (Kaneko et al, 1977).

Hakkinen (1980), in Finland, found a surprisingly high compliance of 74% of a rural population invited to provide gastric aspirates for fetal sulphaglycoprotein. Such high compliance rates are also found for cervical and breast cancer screening in Scandinavian countries (Lundgren, 1979; Hakama et al, 1979).

In the United Kingdom, where screening has focused on endoscopy to the post-gastric surgery group, less than 50% have attended for gastroscopy despite the majority being under regular hospital follow-up (Savage and Jones, 1979; Farrands et al, 1983; Pickford et al 1984).

Attitudes to Cancer and Cancer Screening

For many years it has been apparent behavioural scientists that health activity is not due to one or two sociodemographic factors, but to the sum of the interaction of many perceptive factors and past experiences. Becker (1974) and Cummins et al (1977) have extensively investigated mothers who failed to have their children immunised and developed a model to explain their response or non-response to the preventive approach.

He has termed this model "the health belief model" (HBM) and it takes into account 6 broad factors which determine any health action. These factors are:

1. Readiness to be concerned about health matters.
2. Perception of vulnerability to the illness concerned.
3. Belief about the severity of the illness.
4. Belief about the effectiveness of the treatment.
5. Belief about possible harm or cost.
6. Reaction to cues (e.g. invitations) which might trigger a response.

Only 2 groups have previously examined the role of the HBM in colorectal screening. Dent and Goulston (1980) performed a small study and showed some merit to this approach. Halper et al (1980) examined 1143 subjects at first presentation to the Strang

Clinic, Sloan Kettering Hospital, New York using the HBM questionnaire. They found three basic differences between compliers and non-compliers for the FOB test. Firstly, non-compliers seemed reluctant to see doctors, reported less illness and were less likely to have had a recent medical than compliers. Secondly, non-compliers viewed cancer as more disruptive and life-threatening than compliers and may have been fearful to complete the FOB test whose aim is to detect cancer. Finally, the alteration in diet required for the FOB test was seen as an intrusion into the lives of the non-compliers.

The Strang group are cautious as to the interpretation of their data, but clearly there are different psychological concepts interacting here to determine health activity and that simple concepts of age and sex alone will not readily identify reasons for compliance and non-compliance for screening activities. However, this study has only looked at a very select population who for whatever reasons have still volunteered for a health check-up and do not represent the population as a whole. There is a need, therefore, to in6estigate a more representative group approached during a mass screening programme, using the health belief model, to identify those factors which lead to non-compliance. In this way, new strategies could be devised to make colorectal screening more acceptable to the population at large.

Summary and State of the Art

To date there is no single biochemical marker available to identify pre-operatively an early, curable gastric or colorectal cancer.

Faecal occult blood testing (table 1.9) is plagued by problems including a high false negative rate for colorectal cancers and adenomas with associated variations in false positivity depending on rehydration and dietary factors.

There is conflict as to whether symptom questionnaires have a role to play in the earlier detection of colorectal neoplasia or in the preliminary assessment of patients with dyspepsia to determine priority of investigation to exclude gastric cancer.

Screening for gastric cancer in the Western world is not feasable due to a low prevalence and a falling incidence. Case-finding studies in 'high risk' groups are complicated by such groups being poor indicants of gastric cancer.

Compliance for screening programmes for any common cancer in the UK is low and particularly for FOB testing. The factors affecting the individual's decision to respond to a screening invitation are also poorly understood and researched.

In the following chapters, these areas will be pursued with particular reference to:

(1) the interaction of several biochemical markers to the preoperative detection of gastric and colorectal cancer.

(2) the sensitivity and predictive yields of three guaiac based FOB tests in screening for colorectal neoplasia

Table 1.9

State of the Art in Screening for Colorectal and Gastric Cancer

COLORECTAL CANCER

Haemoccult testing

Rate of Positive slides	1-5%
Predictive Value	18-50%
False positive rate	2-20%
False negative for cancer	9-31%
False negative for polyps	60-75%

Compliance

motivated group	50-85%
non-motivated group	7-48%

GASTRIC CANCER

Low Prevalence and falling incidence in UK

No simple non-invasive screening agent

"High risk" groups are poor indicators of cancer

Low compliance for endoscopic screening in "risk" groups

(3) the development and applicability of a symptom questionnaire to detect gastric and colorectal cancer in the community and 'at risk' groups.

(4) to investigate the factors affecting compliance for cancer screening in the community.

CHAPTER 2
Screening for colorectal cancer and gastric cancer

Introduction

Colorectal cancer screening with Haemoccult as indicated in the introduction has the shortcomings of a high false negative rate, a moderate false positive rate and a low compliance rate.

In order to reduce the false negative detection of cancer with FOB testing two approaches have been proposed; the first to use a questionnaire to detect any symptomatic cancers not producing positive faecal occult blood tests and secondly, to use a more sensitive FOB test.

Schewe et al (1979) proposed the use of a questionnaire to elicit symptomatic cancers and this challenge has been taken up with conflicting results in the United Kingdom. On the positive side, Silman and colleagues (1983) noted that all seven polyps detected in their screening study were symptomatic and that the predictive yield for investigation of an individual with a positive response to one of their nine bowel symptoms (dark red bleeding) was equivalent to that of a positive FOB. Contradicting these results, Farrands et al (1984) found a false negative rate for the questionnaire compared to FOB testing was 83% and the yield of investigation of a positive response to their five item questionnaire was 1.8%, compared with 50% for the Haemoccult test.

Lee and Costello (1982) have advocated the use of a more sensitive guaiac test Fecatest to reduce the false negative rate. In their comparative study of FOB testing with Haemoccult and Fecatest they found that the lesions missed by Haemoccult were indeed detected by Fecatest. However, the positive rate for the Fecatest also rose to 5.8% compared to 2.5% for Haemoccult. They

felt, however, that the positive rate was within manageable limits.

Both these approaches are worthy of further investigation in a screening study and the following account reveals an examination of the value of a self-administered symptom questionnaire on screening for colorectal cancer and also the value of using three guaiac based FOB's of different sensitivities to detect colorectal neoplasia.

Gastric cancer screening in this country does not exist as an entity although studies of post-gastrectomy patients using endoscopy as the screening agent have been performed. Since it is known that early gastric cancer is symptomatic (Fielding et al,1980; Rosch,1981) a survey of upper gastrointestinal symptoms using the questionnaire will also be performed. The data derived from this pilot study will be assessed to determine the possible value of investigating individual 'dyspeptic' symptoms in a similar fashion to the colon studies (Silman et al, 1983; Farrands et al, 1984).

Aims

(1) To produce a valid questionnaire for use in the screening study.

(2) To assess the ability of the questionnaire to detect colorectal neoplasia in the community.

3) To compare the sensitivity and predictive yield of three commercially available FOB tests.

(4) To compare the predictive yield for colorectal neoplasia of the questionnaire and the FOB tests.

(5) To evaluate the potential of a symptom questionnaire to detect upper gastrointestinal disease.

Patients

One thousand and eighty three individuals from 6 urban practices in Leeds were invited over a 15 month period to take part in the study. The subjects were enrolled into the study by one of two methods which will be fully discussed in the compliance section.

Each practice was a group practice with 4-6 partners and together they represent a wide cross-section of the population of Leeds.

(i) Street Lane Practice

This is a 5 man practice serving 11,000 patients in an expensive suburb of Leeds. The majority of the housing is privately owned, with the residents being mainly professional people.

(ii) Slaid Hill Practice

Four GP's serve 4,000 patients. The majority of these subjects are business owners or professional people, who own their houses.

(iii) Burmantofts Health Centre

This practice comprises 4,500 patients served by the same 4 GP's as the Slaid Hill practice. The patients are mainly housed in high-rise flats which are rented from Leeds Corporation. There is a high level of unemployment in this practice.

(iv) Shaftesbury Health Centre

Six GP's serve 13,000 patients. There is a high level of unemployment within this practice, which covers a corporation

housing estate that has the third highest crime rate in the United Kingdom.

(v) Chapeltown Health Centre

This practice of 9,000 patients is served by 5 GP's. A high proportion of the patients are Asian or West Indian. Unemployment is high and few individuals own their houses.

(vi) Meanwood Health Centre

Six GP's serve 13,000 patients. There is a very broad mix of social class groups in this practice.

Criteria for entry to study

Each subject was required to fulfil four requirements to enter the study. He/she should be aged between 50-70 years, not have any previous history of gastrointestinal malignancy or be on any medication for GI disease and finally, at the time of presentation to have had no recent consultation with his/her GP with GI symptoms.

Detection of Neoplastic Disease

(1) Agents

(a) Faecal Occult Blood Testing

3 commercially available guaiac based FOB tests, Haemoccult, Fecatest and Hema-chek, were used in this study.

The Haemoccult (Eaton Laboratories) package contains 3 cardboard test envelopes with 6 applicators for taking samples of stool. On three consecutive days the patient takes a pea-size sample from two parts of the stool and spreads them onto the two red-framed openings inside the test envelope. If the patient misses a day he is requested to take samples from his next stool.

The three envelopes are then returned for testing.

No dietary restriction, other than reduction of Vitamin C intake is required when using Haemoccult. No rehydration prior to testing is required. A positve test is defined as the presence of a blue colour within 30 seconds (Fig 2). Cost:- £1.50

Hema-chek is similar to Haemoccult in that two separate samples from three motions are required for testing. However dietary restriction is recommended for two days prior to testing and also during the collection of the samples. The subject should not eat meat, turnips, horseradish or medicines containing aspirin or Vitamin C. He may eat small amounts of chicken, tuna fish, peanuts and bran cereal and is permitted lots of vegetables and fruit. Rehydration with one drop of water immediately prior to testing is also recommended. A positive test is the appearance of a blue colour on the slide within 30 seconds. Cost:- £ 1.25

Fecatest is supplied as a well designed package containing three robust plastic containers for the sample collection (Fig 1). Only one sample per day on three days is required. Due to the extreme sensitivity of the test strong emphasis is placed on the dietary restrictions listed above being adhered to in order to reduce any false positive tests. No rehydration is required unless the specimen is dry and the guaiac paper is unmarked when one drop of water should be applied to the sample before testing. Cost:- £1.75

Each individual received one of the packages and was given counselling on diet and instructions for completion of the test. Haemoccult was available at the commencement of the study and was

extensively used. When Fecatest and Hema-chek became available then each agent was used for a 4 week period in rotation.

On completion of the package the patient returned the FOB's in the prepaid envelope to St. James's University Hospital for testing. The author performed all the tests. Any blue discoloration on the addition of the hydrogen peroxide within the 30 second period constituted a positive test (Fig 2) requiring full assessment by digital examination of the rectum, proctoscopy, fibreoptic sigmoidoscopy and double contrast barium enema.

(b) Symptom Questionnaire

The questionnaire consisted of 41 questions. These dealt with 18 specific gastrointestinal symptoms as well as 8 genito-urinary and cardio-respiratory questions. Past medical history, drug history, family history of stomach and bowel disease were also included as any symptom responses gained may be influenced by these factors or their interpretation altered. Specific questions relating to smoking, alcohol and arthritis were included as they not only have an aetiological impact on GI disease but can also produce variations in the levels of tumour markers.

The final choice of questions was derived from a number of sources. Other questionnaires in observed use were reviewed in particular the Cornell Medical Index (Brodman, 1951), the Strang Clinic questionnaire (courtesy of Dr. Helen Miller) in the United States and the questionnaires used by Grumpel and Mason (1974) and by Silman et al (1983) in this country. A number of questions were derived and modified from these. Following discussions with colleagues in the Department of Surgery at St. James's University

Hospital several new questions were devised for final inclusion.

The format selected was a deliberately simple one. Each question was followed by two boxes in which according to the answer reqired a tick is placed to indicate yes or no. This closed format of question only allowing one or other response was felt to be the simplest available and therefore most valid for general use. It would be possible to answer only 36 questions as a negative response to certain questions lead to missing out the next question.

Methodology

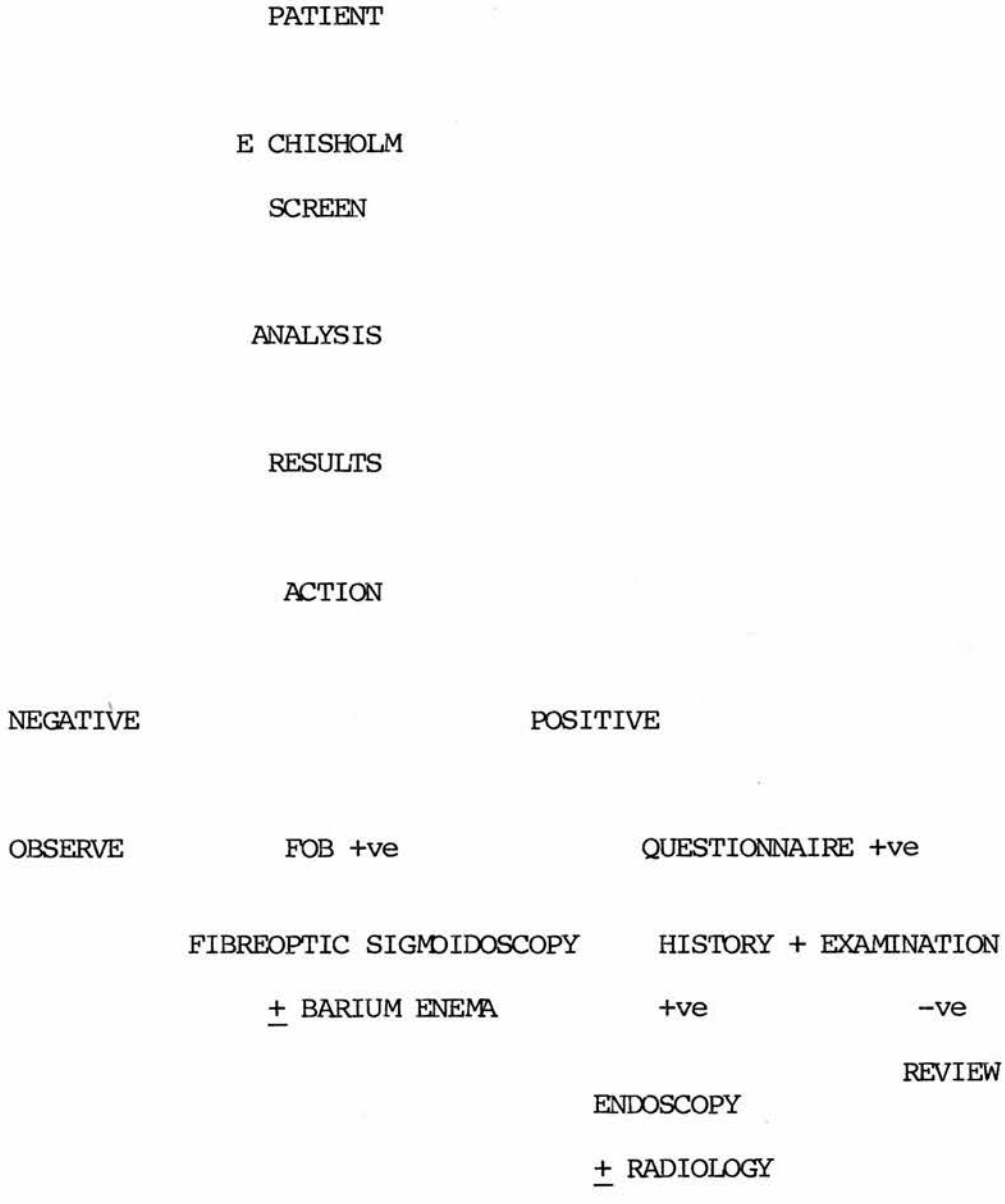
The general scheme is shown in the flow diagram opposite (fig 3). Each subject completed the questionnaire to the best of their ability at the time of consultation. Any person unable or unwilling to complete the form was then asked the questions by the investigator but a note was made that this was a failure of the method.

Any symptoms elicited by the questionnaire were expanded upon at this time. A record was then made in a logbook as to whether in the investigator's opinion the patient would require further assessment of these symptoms. These individuals would be reviewed in a further 4 weeks and if still symptomatic were offered appropriate investigation.

Instructions for the completion of the FOB tests were also given at this time plus appropriate dietary advice. The specimens were then returned to the author for testing in the stamped addressed envelope provided.

Figure 3

Flow diagram of screening schedule



No action was taken where the results were considered normal. For patients with positive results, further consultation was arranged in the GP's surgery to review any symptoms and to discuss the need for further investigations.

Suspected bowel disease was assessed by digital examination of the rectum, proctoscopy and fibreoptic sigmoidoscopy. All patients with a positive FOB also underwent double contrast barium enema. Those with upper GI symptoms either were subjected to gastroscopy or appropriate radiological studies. All endoscopies were performed by the author.

Diagnosis and Treatment of Neoplastic Disease

All biopsy specimens were reported by the Pathology Department at St. James's Hospital. Any patient found to have an adenomatous polyp was referred for colonoscopic poylpectomy and malignancy was dealt with as indicated by routine clinical criteria.

Follow-up of screened individuals

Each subject was flagged for instant notification to the investigator of the diagnosis of cancer via the Regional Cancer Registry. Regular review of the pathology reports of newly diagnosed GI cancers was undertaken to identify any false negative cases for the study and all the GP records have been personally reviewed by the investigator at one year.

Validation of the questionnaire to elicit symptoms.

The questionnaire underwent a pilot study to determine its validity before general use in the screening situation. Validity in this context was felt to encompass five aspects: (i) to be acceptable to the population under study; (ii) to be easily completed; (iii) to be consistent i.e. responses are similar to those gained in a conventional doctor-patient interview; (iv) to be reproducible when elicited on two separate occasions; (v) to be of value or use when complete. The steps taken to validate this questionnaire are now described. A copy of the questionnaire is printed opposite and in Appendix A.

Patients

144 subjects were enrolled and divided into 3 groups: 69 were 'normal' individuals who were not attending hospital clinics and who were aged over 50 years; 40 subjects were inpatients with proven benign gastrointestinal conditions and 35 individuals had proven GI cancer.

Questionnaire

As indicated above the format of the questionnaire was a series of closed questions followed by two boxes. A tick in the appropriate box indicated either a positive or negative response.

Methods

All 144 subjects were required to complete the questionnaire unaided to assess its acceptability and feasability of completion. A test-retest system was used to assess the reproducibility of the responses, 20 subjects being required to complete a second questionnaire after a 2 week interval.

THE DEPARTMENT OF SURGERY AT ST. JAMES'S HOSPITAL IN CONJUNCTION WITH LOCAL G.P.'s IS TRYING TO COMPOSE A SIMPLE FORM OF QUESTIONNAIRE WHICH WILL LEAD TO EARLIER DETECTION OF VARIOUS DISEASES

COULD YOU PLEASE FILL IN THE QUESTIONNAIRE AS BEST YOU CAN, TAKING YOUR TIME AS THERE IS NO HURRY. IF YOU ARE NOT SURE OF ANYTHING OR THE QUESTIONS ARE NOT CLEAR, DO NOT ANSWER THAT QUESTION

PLEASE FILL IN A FEW PERSONAL DETAILS. ALL ANSWERS WILL BE ENTIRELY CONFIDENTIAL

NAME.....AGE.....SEX M/F
(FORENAME) (SURNAME)

ADDRESS.....OCCUPATION (If you are unemployed or retired, please give former occupation)

.....

.....

.....

.....

THE FOLLOWING QUESTIONS PROVIDE USEFUL BACKGROUND KNOWLEDGE ON THE STATE OF YOUR PAST HEALTH AND YOUR FAMILY'S HEALTH

MOST QUESTIONS REQUIRE YOU TO PLACE A TICK IN THE CORRECT BOX OPPOSITE THE QUESTION

PAST HEALTH	YES	NO
HAVE YOU EVER ATTENDED A HOSPITAL OUTPATIENT CLINIC?	[ ]	[ ]
HAVE YOU EVER BEEN A PATIENT IN HOSPITAL?	[ ]	[ ]

If YES to either question, please give a few details

.....

.....

HAVE YOU EVER HAD AN OPERATION ON YOUR STOMACH, BOWEL OR GALLBLADDER?	[ ]	[ ]
DO YOU HAVE SUGAR DIABETES?	[ ]	[ ]
DO YOU SUFFER FROM ARTHRITIS?	[ ]	[ ]
DO YOU SUFFER FROM ASTHMA?	[ ]	[ ]
ARE YOU BEING TREATED FOR RAISED BLOOD PRESSURE?	[ ]	[ ]

TREATMENT

DO YOU TAKE ANY MEDICINES/TABLETS REGULARLY?	[ ]	[ ]
ARE THESE FOR STOMACH OR BOWEL PROBLEMS?	[ ]	[ ]

If YES, please name them.....

.....

SMOKING AND DRINKING

Both smoking and drinking can affect your health. Please answer the following questions

DO YOU SMOKE?	[ ]	[ ]
HAVE YOU EVER SMOKED, BUT HAVE SINCE STOPPED	[ ]	[ ]

PLEASE STATE AVERAGE AMOUNT SMOKED.....
(If you have given up, state average amount before stopping)

PLEASE RECORD AVERAGE ALCOHOL INTAKE.....
(e.g. 3 pints/night, 2 glasses wine/week)

FAMILY HISTORY

Some diseases run in the Family, e.g. Asthma, sugar diabetes

ARE THERE ANY DISEASES THAT RUN IN YOUR FAMILY?	[ ]	[ ]

If YES, please give details.....

.....

HAVE EITHER OF YOUR PARENTS OR BROTHERS OR SISTERS HAD AN OPERATION ON THEIR STOMACH, BOWEL, BREAST? If YES, please give details as best you can	[ ]	[ ]

.....

.....

Please turn over

THE FOLLOWING SECTIONS ARE RELATED TO YOUR HEALTH AT PRESENT

PLEASE TICK THE BOX THAT SEEMS MOST SUITED TO YOU

IF YOU ARE ASKED TO GIVE DETAILS, TRY TO BE BRIEF

SECTION A	YES	NO
HAS YOUR APPETITE CHANGED RECENTLY?	[ ]	[ ]
If YES, has it DECREASED?	[ ]	[ ]
HAVE YOU LOST WEIGHT RECENTLY?	[ ]	[ ]
ARE YOU ON A DIET?	[ ]	[ ]
DO YOU HAVE DIFFICULTY SWALLOWING FOOD?	[ ]	[ ]
DO YOU FEEL THAT FOOD STICKS BEFORE REACHING YOUR STOMACH?	[ ]	[ ]
ARE YOU TROUBLED BY BURNING OR DISCOMFORT BEHIND THE BREAST BONE?	[ ]	[ ]
HAVE YOU EXPERIENCED ANY NAUSEA (feeling sick) OR VOMITING (being sick) RECENTLY?	[ ]	[ ]
DO YOU HAVE ANY PAIN OR DISCOMFORT IN THE ABDOMEN (Tummy)?	[ ]	[ ]
IF YES, IS THIS DIFFERENT FROM PREVIOUS TUMMY UPSETS?	[ ]	[ ]

Please give details.....

.....

SECTION B

A FEW QUESTIONS RELATED TO YOUR BOWEL HABIT NOW FOLLOW

HOW OFTEN DO YOU OPEN YOUR BOWELS (e.g. once alternate days).....

AFTER YOU HAVE EMPTIED YOUR BOWELS DO YOU FEEL YOU STILL NEED TO GO?	[ ]	[ ]
HAS THERE BEEN A RECENT CHANGE IN THE FREQUENCY OF YOUR MOTIONS?	[ ]	[ ]
HAS THERE BEEN A CHANGE IN THE APPEARANCE OF YOUR MOTIONS?	[ ]	[ ]
DO YOU HAVE EPISODES OF YOUR MOTIONS BEING LOOSE THEN BECOMING NORMAL AGAIN?	[ ]	[ ]
HAVE YOUR MOTIONS BECOME MORE CONSTIPATED?	[ ]	[ ]
HAVE YOU NOTICED ANY BLOOD IN YOUR MOTIONS?	[ ]	[ ]
HAVE YOU EVER NOTICED SLIME IN YOUR MOTIONS?	[ ]	[ ]

Please turn over

SECTION C

THIS IS THE LAST SECTION TO BE COMPLETED. AS BEFORE PLACE A TICK IN THE APPROPRIATE BOX

	YES	NO
DO YOU HAVE A COUGH MOST DAYS?	[ ]	[ ]
HAVE YOU EVER COUGHED UP BLOOD?	[ ]	[ ]
DO YOU SUFFER FROM PAIN OR DISCOMFORT IN YOUR CHEST?	[ ]	[ ]
DO YOU HAVE TO GET UP AT NIGHT TO PASS WATER?	[ ]	[ ]
IF YES, IS THIS MORE OFTEN IN THE LAST SIX MONTHS?	[ ]	[ ]
DO YOU HAVE ANY DIFFICULTY PASSING WATER?	[ ]	[ ]
HAVE YOU EVER NOTICED BLOOD IN YOUR WATER?	[ ]	[ ]
HAS THERE BEEN ANY CHANGE IN COLOUR OF YOUR WATER RECENTLY?	[ ]	[ ]

If YES, please give details.....

.....

.....

TO BE COMPLETED BY WOMEN ONLY

DO YOU STILL HAVE YOUR PERIODS?	[ ]	[ ]
IF NO, HAVE YOU NOTICED ANY BLOOD OR BROWN DISCHARGE FROM FRONT PASSAGE?	[ ]	[ ]

Twenty three symptomatic patients completed a questionnaire before being interviewed in the routine manner by a consultant clinician. To determine the consistency of the responses on the patient's questionnaire, the clinician then completed an identical questionnaire on the basis of the interview without reference to the patient's form. The two forms were then compared using Kappa statistics.

Statistical Method

Since the possibility of chance agreement between two series of replies to the same set of questions varies according to the incidence of positive and negative replies to the individual questions, the Kappa (K) statistic was calculated to adjust for the contribution of chance agreements. Kappa is calculated according to the formula, $K = (Po-Pe)/(1-Pe)$, where Po is the observed proportion of agreement and Pe is the proportion of expected agreement from chance and calculated from the marginals in a two by two table. The values for Kappa vary from +1.0 where there is total agreement to -1.0 where there is total disagreement. A value of 0 corresponds to chance agreement alone.

Results

Acceptability

One subject refused to complete the questionnaire.

Feasability

Three subjects failed complete the questionnaire due to poor eyesight or dyslexia. The average time to completion was 7 minutes (range 4-10 minutes). The completion rate for the

questionnaire was 96% of all questions.

Reproducibility

In all three groups the test-retest study showed only one answer was altered in one questionnaire and this related to family history. Thus only one response was changed out of a possible 1,440 answers.

Consistency

In the study which compared responses obtained on the questionnaire with those obtained by the consultant clinician, Kappa statistics were applied to the 18 GI symptoms. In 15 questions there was a close correlation of answers and the K values all exceeded +0.85. However with three questions, namely those designed to elicit responses concerning tenesmus, early satiety for food and new episodes of abdominal pain, the K values were +0.2, +0.125 and +0.3 respectively. The remaining general questions all had K values =+1.0.

Applicability

When the responses to the gastrointestinal questions were compared between the three groups of subjects, the number of positive responses was naturally greater in the hospital referred groups. Fifty four of 65 subjects (82%) in the 'normal' group had zero or one positive response, with seven having three or more positive responses. In the group with cancer 33 of 35 (94%) had three or more positive responses, as did 33 of 40 (82%) individuals in the benign disease group (table 2.1).

Follow-up assessment of the seven 'normal' subjects revealed that one had a confirmed diagnosis of ulcerative colitis

Table 2.1

The distribution of positive gastrointestinal responses by group

No. +ve responses	"Normal" (n = 65)	Benign (n = 40)	Cancer (n = 35)
0	39	0	0
1	15	3	0
2	4	4	2
> 3	7	33	33

and was experiencing a relapse of symptoms, two were treated with H2 blockers for dyspeptic symptoms when reviewed by their GP and three were referred for investigation of rectal bleeding and were found to have haemorrhoids. The remaining individual, who had right-sided pain, loose altered stools, nausea and change in the colour of his urine was diagnosed as having choledocholithiasis on ultrasound examination.

The results of the pilot study produced the conclusion that three questions in the GI section needed re-wording and re-piloting. However the questionnaire was relatively easy to complete, could elicit GI symptoms consistent with a clinician, could accurately identify subjects with established GI disease and finally, as was desired for the main screening study, the questionnaire could highlight normal subjects with symptoms as yet unreported to a doctor, which merited further investigation. In particular, any subject with three or more positive responses to the GI questions in the main study would appear to be at risk of harbouring gastrointestinal disease. Equally important is the value of a negative response which on the reproducibility study showed one alteration in 1,440 possible responses, implying a low risk of sypmtomatic false negative disease in the screening study.

Results of Main Study

Questionnaire Results

724 questionnaires were available for analysis from the main GP group. The questionnaire was completed unaided by 609 individuals; a further 63 attempted the questionnaire but had difficulty completing the form due to poor eyesight (lack of reading glasses). Only 52 subjects made no attempt to complete the questionnaire, the majority being elderly women from the inner city practices. In these cases the investigator completed the questionnaire for the individual.

The rate of completion for the questionnaire in the 609 cases was greater than 90% of all items. 95% of the gastrointestinal symptoms were completed, maintaining the high levels found in the pilot study.

The most common symptom elicited in the GP group was that of episodic looseness of the bowel motion (26%) followed by heartburn (23.8%). The least common symptom elicited was difficulty in swallowing food (2.45%) and that was most commonly seen in patients presenting with sore throats (Table 2.2). The frequency of the remaining symptoms in the population is shown in table 2.2.

Although 74 subjects had noticed blood in their motion, only 10 had noticed this within the past 6 months. Four of these had not reported this to their GP and were subsequently investigated. One subject of the 74 noted dark red 'blood' in the motion and was also investigated.

It was found that overall 238 (27%) of the group had three

Table 2.2

Frequency of positive responses per question in the general practice group

	No.	%
Reduced Appetite	55	6.75
Wt loss, no diet	35	4.3
Difficulty swallowing	20	2.45
Food sticking	42	5.24
Heartburn	192	23.76
Nausea	101	12.48
Pain/discomfort	143	17.85
New pain	61	10.34
Bowel habit	32	4.03
Incomplete emptying	66	8.12
Altered stool frequency	50	6.17
Altered stool appearance	59	7.3
Looseness	212	26.1
Constipation	112	13.9
Blood	90	11.3
Slime	57	6.99

or more positive GI responses, and that 5% had 6 or more symptoms present. Since it would be clearly impossible to investigate all subjects with three or more positive responses, all such individuals were interviewed by the investigator and a decision reached on the basis of his clinical judgement. In this way 38 individuals were investigated for upper or lower G.I. symptoms to exclude malignancy. 9 subjects underwent upper GI endoscopy and 29 fibreoptic endoscopy (9 also had a positive faecatest) and barium enema.

Three patients undergoing gastroscopy had no lesion detected in the oesophagus, stomach or duodenum. Random biopsies were also normal in these individuals. 2 duodenal ulcers, 1 gastric ulcer and 2 hiatus herniae with oesophagitis and one bile gastritis were found in the remaining 6 subjects.

During the investigation of the individuals with large bowel symptoms diverticular disease was found most commonly (13 cases). In 2 further cases haemorrhoids were discovered, drug induced colonic inertia in one and in 3 no lesion was detected, although spasm of the bowel during endoscopy reproduced their symptoms. These patients were subsequently labelled as having the irritable bowel syndrome following normal barium enemas. In 6 subjects no explanation was found for their symptoms.

Whilst two hyperplastic polyps and one adenomatous polyp (4 mm dia) were found coincidentally at fibreoptic sigmoidoscopy no significant neoplastic disease was found giving an overall 4.12% investigation rate with a predictive yield for neoplasia using the questionnaire of zero. Only one person to date has

presented with a GI malignancy (pancreatic cancer) but she had no symptoms of gastrointestinal dysfunction for 15 months following screening.

F.O.B.'s

Six hundred and eighty three fully completed FOB packages, 460 Haemoccult, 127 Fecatest and 96 Hema-check, were returned out of a total of 724 (94.6%). The number of positive packages is tabulated below along with the percentage positivity rate, findings on investigation and the predictive yield per type of FOB for neoplasia (Table 2.3).

Haemoccult testing revealed one carcinoma arising in an adenomatous polyp of the sigmoid colon and this had breeched the muscularis mucosa. Colonoscopic snare of the polyp had been performed and as there was no evidence of lymphatic or venous invasion and the cells were well-differentiated no further treatment was given except routine follow-up by endoscopy. In two further subjects adenomatous polyps were detected. One subject had a sigmoid polyp 1 x 1.5 cm and a caecal polyp 1.5 cm x 1.5 cm removed by snare polypectomy and in the remaining subject a 2 cm adenomatous polyp was removed endoscopically from the descending colon. All 3 individuals were FOB positive on one day only.

Unfortunately, 3 individuals refused to have any investigation for positive Haemoccult findings, despite being made fully aware of the risks of neoplastic disease being present. To date no patient has presented during the follow-up period with symptoms or signs of bowel disease. In the remaining 6 cases investigated for bowel disease, 4 cases had diverticular disease

Table 2.3

Results of Faecal Occult Blood Tests

FOB	No. Positive	% +ve	Neoplastic	Yield
460 Haemoccult	12	2.6	1 polyp cancer,3 polyps	33%
127 Fecatest	16	12.6	No Neoplasia	0%
96 Hema-chek	1	1.04	1 Dukes'B cancer	100%

noted and 1 case of haemhorroids was found with no radiological or endoscopic abnormality. Repeat FOB's in these patients at 6 weeks were all negative.

None of the 12 subjects positive on Haemoccult testing had a positive symptom response on the questionnaire, nor did they on subsequent review own up to any symptoms.

As shown in table (2.3) Fecatest proved to have the highest positive rate almost 5 times that of Haemoccult. Whilst the positive rate was recorded as 12.6% (16 subjects) in fact six other subjects had initially had positive Fecatest slides but they had not adhered to the dietary advice. On retesting with dietary restriction, they were all negative for both Fecatest and Haemoocult and so not investigated. To date none of these six have presented with gastrointestinal disease. Nine of these 16 Fecatest positive individuals were also symptomatic for colonic disease (8) or for upper GI disease.

No neoplastic disease was detected by Fecatest. In 11 subjects diverticular disease was found, 2 subjects had haemorrhoids, one a duodenal ulcer and in two remaining subjects no disease was detected at endoscopy or on barium enema.

Hema-chek revealed one asymptomatic Dukes' B cancer of the sigmoid colon. 2 of the six slides, both on the same day, were positive. This lesion was polypoidal in appearance on endoscopy, confirmed at laparotomy and was 2.5 cm x 1.5 cm in size with well differentiated cells histologically.

Discussion

The faecal occult blood tests have again shown their ability to detect early colorectal cancers and significant sized colorectal polyps. However, it is clearly seen that the differences in sensitivities of the three guaiac based kits are quite different. The positivity for Haemoccult in this series (2.6%) is comparable with other screening studies (Hardcastle et al 1983; Silman et al 1983) and the positive rate for Hema-chek (1.04%) is encouraging although the number investigated with this test is extremely small. Fecatest, however, has shown itself in this study to be quite unsuitable for screening with a positive rate of 12.6% (after 6 had repeated the test with proper dietary restrictions). This rate lies between that experienced by Berretta et al (1980) and Feneyrou et al (1982) (50% and 30% respectively), and that of Lee and Costello (1982; 1983) where a 5%-8% positivity rate was encountered.

Furthermore the predictive yield for Fecatest was 0% compared with 33% for Haemoccult. Clearly random chance will affect the yield of tumours and the detection of 2 cancers in 683 patients equates with Hardcastle's rate of 3.3 per 1000 screened aged over 45 years (Hardcastle et al, 1983). Whilst any of the neoplasms could have just as easily fallen in the Fecatest group, by comparing the predictive yield it is further apparent that the relative superiority of Fecatest in comparative studies of diagnosed cancers (Farrands and Hardcastle 1984; Turunen et al,1984) bear little relation to the screening situation. Indeed Armitage et al,(1985) found that screening using Fecatest and a

special FOB kit with Fecatwin S and FECA-EIA (an immunological test to reduce the false positive cases) had a prohibitively high positive rate. No direct comparison can be made between the FOB kits since it was felt that the compliance for stool testing would be reduced if double the amount of stool samples would have to be taken by completing two tests at the same time.

In view of the small numbers of individuals involved, no comment can be made as to the potential of FOB tests for reducing mortality from colorectal cancer but the diagnosis of a Dukes' A and B cancer is in line with most screening studies where a predominance of early stage cancers has been found.

The questionnaire has provided interesting data on the prevalence of gastrointestinal symptoms experienced by the general population. To ensure the validity of the responses the pilot study was performed and proved a valuable exercise. As indicated three questions, whilst used in other questionnaires, were found to be invalid in our screening questionnaire. This supports Oppenheim's (1978) point that all questions should be piloted before general use.

As with the pilot study, the questionnaire was acceptable to the public who expected to be asked health and symptom related questions as part of a screening programme. The pilot study had indicated that some would be unable to complete the questionnaire due to visual problems but few refused to attempt to complete the questionnaire (3.2%) and the general rate of completion was staggering with over 90% of the questions being answered.

Unfortunately, in the main study the number of positive

responses to the GI questions was considerably higher than in the pilot study. Even using the arbitrarily contrived cut-off point from the pilot study more than 27% had three or more positive responses. It became rapidly clear in the study that not all these individuals could be investigated nor did they merit investigation for colorectal symptoms where the FOB's were usually negative. Thus, remembering that a screening test is not diagnostic in itself but an indicator of potential risk and that some form of further assessment is required, the author opted to accept the questionnaire as a filter to draw attention to possible symptomatic cancers. Using a standard clinical history and examination a clinical decision was made to investigate or not on this basis. As shown in the results no colorectal neoplasm was identified in this way, although benign conditions were found. No new case of colorectal cancer has come to light from either the regional cancer registry or from surveillance of the pathology reports in St James's University Hospital to date.

The incidence of lower GI symtoms in the study is very similar to that seen by Farrands and Hardcastle (1984) and reflects the work of Jones (1976) and Thomson and Heaton (1980) and so it is not surprising that 29 individuals were investigated with no benefit. In only one subject was the symptom of dark red blood encountered and on full colonoscopy no lesion was found. This is in direct contrast with Silman et al (1983) who had found this symptom to be common and to have a predictive yield for neoplasia equal to Haemoccult. However Chapuis et al (1985) found a predictive yield on investigation of rectal bleeding as a first

presentation in middle age was 8% for sigmoid and rectal neoplasms.

The final problem in this study was that all the neoplastic lesions detected on occult blood testing were asymptomatic on two occasions during the assessment period. This also confirms the 83% false negative rate for the symptom questionnaire of Farrands and Hardcastle (1984) where the predictive yield for a symptom in that study was 0.78%.

The prevalence of upper GI symptoms within the population must also be high with the incidence of heartburn in this study alone being 24%. The potential of a simple symptom questionnaire to detect gastric cancer would therefore seem limited in the extreme. In the period of this study only nine individuals were investigated for worrying symptoms and whilst new peptic ulceration was detected the whole time pursuit and investigation of upper GI symptomatic individuals with minimal symptoms in a screening setting does not seem feasible from the pilot study. This is in conflict with arguments proposed by Gear and Barnes (1980) and Allum et al (1986) and will be examined in greater detail in the chapter on symptomatic detection of colorectal and gastric cancer.

The principal conclusion of this study is that the addition of a symptom questionnaire to elicit lower GI symptoms in combination with FOB testing confers no advantage to screening for colorectal cancer. On the contrary, its use does in fact reduce the cost effectiveness of any potential screening programme by increasing the investigation rate for no additional neoplastic

yield.

It is further noted that Fecatest was too sensitive in this study to be of value in any future colorectal cancer screening programme.

Finally, the existence of considerable upper GI symptoms precludes any attempt at repeating the approach of Silman et al (1983) and Farrands and Hardcastle (1984) using a single symptom to indicate potential risk for the presence of early gastric cancer as opposed to colorectal cancer.

Looking to the future, any major developments in the performance of the screening agent for colorectal cancer must lie with the production of a more reliable FOB test. The most likely source of success would seem to lie with the immunological differences between human haematin and the presence in food of cross-reactive substances rather than with more sensitive guaiac tests (Armitage et al,1985). Attention to simpler aspects of FOB testing may favourably influence the false positive rate of Haemoccult. Elliott et al (1984) invited any subjects with a positive FOB to complete a second FOB test under strict dietary restriction. Investigation of only those positive on a second occasion were investigated. In his study Elliott and his colleagues (1984) had an initial positive reaction in 99 cases which then fell to 32 on strict dietary control second time round. Twelve cancers were found, 9 Dukes' stage A. The predictive yield was increased by this approach and there were no false negative cancers on review in this study. Six day testing may also reduce the false negative cases missed by Haemoccult and deserves further

prospective evaluation. There appears to be little to offer in the way of screening for gastric cancer other than surveillance of high risk groups (Cuschieri, 1986) or the earlier investigation of dyspeptic patients by endoscopy which will be assessed in chapter 4.

CHAPTER 3

Factors affecting screening compliance

Introduction

The cost-effectiveness of any screening agent is dependent upon two variables - the validity of the agent itself and the acceptability of the agent to the target population. In the previous chapter the value or otherwise of screening agents for colorectal cancer principally was considered and in this chapter factors affecting compliance for a screening invitation including FOB testing will be studied.

Jocelyn Chamberlain (1982) has stated that a compliance rate of 80 - 85% for faecal occult blood testing would be required to make colorectal cancer population screening viable. However as shown in Table (3.1) that goal has never been attained in randomly selected groups in the United Kingdom. As shown in the table where some input has been given by the screening promoters (Silman et al 1983; Lee 1983) compliance can be raised above the average response to a simple postal invitation to screen. However the workplace is not the ideal situation for population screening in terms of the distribution of the workforce in too many outlets.

An appraisal of the factors producing compliance and non-compliance is clearly necessary to seriously consider FOB screening in the United Kingdom. If one was to simply list the likely causes of failure to comply with screening three reasons might suggest themselves. Firstly, the test is unacceptable to the target population, secondly the way screening is promoted by the medical profession is poor and insufficient to overcome the final factor, a resistance on the part of the public to preventive medicine measures. This would appear to be a major, yet

Table 3.1

UK Screening Experience

Author	Promotion	Compliance (%)
Hardcastle 1980	Postal	45
Farrands 1981	Postal	29
Millions 1982	Postal and District Nurse	33
Hardcastle 1983	Postal	37
Lallemand 1984	Postal (Collect from GP Practice)	42
Lee 1983	Occupational	42
Silman 1983	Occupational	50

unquantified, factor to which failures of compliance for the common cancers and immunisation programmes have been ascribed.

In the following studies, the role of the G.P. in promoting screening and the acceptability of several screening tests will be assessed. Whilst designing such variations in screening packaging may be relatively straightforward, measuring the attitudes of the population to preventive health measures requires the expertise of the behavioural psychology approach. Becker (1974) and his associates (Cummins et al,1978), have recorded the mothers' responses to immunisation therapy and as a result formulated a model of behaviour, the Health Belief Model, to explain compliant and non-compliant behaviour.

This model formulates that health behaviour is dependent on the sum of the interaction of six variables or scales in the model described as the following:-

i. Readiness to be concerned about health matters
ii. Perception of vulnerability to illness
iii. Perception of the benefits/barriers to health action
iv. Knowledge of the illness concerned
v. Perceived severity of illness
vi. Reaction to cues (e.g. invitations).

At the outset of this research, only two limited studies (Halper et al 1980, Dent and Goulston 1980) have been reported using this approach. It was therefore felt that an assessment of the populations attitudes to health, illness and screening for cancer in the United Kingdom may be of value for planning future screening strategies.

Aims

To assess the influence of the General Practitioner in the promotion of FOB testing.

To record the attitudes of the population to health, illness and cancer prevention by use of the Health Belief Model.

To determine if there are consistent differences in the attitudes of compliant individuals to non-compliant subjects in a screening study.

Materials and Methods

Patients

Individuals aged between 50 and 70 years old and not currently complaining of or on medication for GI symptoms were eligible for study. They were recruited by two methods discussed below from the six general practices in the Leeds East Area, as described in chapter 2.

Agents

Each individual was required to complete a 41 item self-administered symptom questionnaire (see chapter 2), give blood for tumour marker estimation and return by post a three day faecal occult blood test.

To assess the population's attitudes to health, illness and preventive medicine a 71 item self-completed questionaire was developed and modified following a pilot study based on the Health Belief Model (Cummins et al 1978). This questionnaire shown in full in subsequent pages comprised six scales to measure general health belief, perceived vulnerability to illness, benefits and barriers to health activity, attitudes to medical services, knowledge of cancer and perceived severity of illness. Basic demographic data inluding age, level of education and smoking was also recorded.

Enrollment

Two methods were used to assess the role of the G.P. in promoting FOB testing, a direct 'case-finding' exercise and a second indirect 'screening' approach.

In the following sections we would like you to read some statements about health problems, and indicate by circling one of the alternative answers how far you personally agree or disagree with the statement. There are no right or wrong answers; just give your opinion. Please circle ONE answer only for each question.

SECTION A

1. It is more important to have a good life now, than worry about future health.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

2. Physical fitness is important to me.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

3. People can't really do a lot to prevent illness.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

4. Illness always gets me down.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

5. Fit people get as many illnesses as everyone else.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

6. I usually eat what I know is good for me.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

7. Regular medical check-ups are useless unless you are ill.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

8. Good health or bad health is something you just have to put up with.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

9. I think that people are fanatical about health these days.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

10. Six monthly check-ups at the dentist are a waste of time.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

SECTION B

1. In general I enjoy good health

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

2. I am unlikely to suffer from a serious illness in the future.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

3. If I wait long enough, I will get over most illnesses by myself.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

4. I am the type of person who worries a lot about their health.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

5. I take ages to recover from illness.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

6. I go to the doctor the minute I feel unwell

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

7. I don't suffer from colds and flu as much as other people

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

8. I always have a well stocked medicine cabinet at home

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

9. I worry a lot about getting cancer

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

10. My health will probably always be below par

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

SECTION C

1. There is nothing I can do to prevent illness from happening

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

2. Finding a disease early makes no difference to the success of treatment

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

3. I am too old to worry about having health check-ups

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

4. A person can have a serious illness and not know it

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

5. Having a medical check-up usually stirs up trouble

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

6. I'd be frightened to have a check-up in case something was found

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

7. Certain medical tests can show up a problem you did not know about

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

8. I'd be prepared to give up my time if I could have a free medical check-up with my G.P.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

9. There is no point in having a check-up if you have been well all your life.

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

10. Having a regular check-up for cancer is a good idea

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

SECTION D

1. I have great faith in modern medicine

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

2. Nurses and doctors always do what's best for you

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

3. I often feel confused after visiting the doctor

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

4. I can never see the doctor when I want

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

5. Doctors don't listen enough to their patients

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

6. It is important do <u>exactly</u> what the doctor says when I'm ill

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

7. There's a lot doctors don't know about most common illnesses

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

8. Doctors should spend more time telling their patients how to stay healthy

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

9. I don't like visiting hospitals

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

10. I worry about having to go into hospital

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

SECTION E

The next sections relate specifically to cancer. Your answers to the following statements are important as they will help us to make our cancer prevention programme more attractive to patients in our practice.

1. You can have cancer and not know about it

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

2. Finding cancer early leads to a better chance of cure

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

3. Tests can detect cancer before you feel unwell

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

4. No matter where you find cancer there is always a poor outcome

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

5. Cancer just about always means death

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

6. The treatment for cancer is worse than the disease itself

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

7. Having cancer is the worst thing that can happen to anyone

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

8. Some types of cancer can be cured more effectively than others

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

9. If I had cancer I would want to be told

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

10. If I thought I had cancer I would put off going to see the doctor about it

(a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
(f) I completely disagree

This section asks in more detail about personal experience of cancer. If you have not known anyone with cancer, please proceed to Section F below.

1. Do you know anyone who has had cancer (a) Yes
(If the answer is no please proceed to the next section (b) No

2. Do you know anyone who has been cured of cancer (a) Yes
(b) No

3. Have you heard of either cancer of the stomach or bowel? (a) Yes
(If no please go on to the next Section below) (b) No

4. Has a relative or friend had either of these cancers? (a) Yes
(b) No

5. Did this greatly upset their way of life? (a) Yes
(b) No
(c) Don't know

6. Do you think you can have either of these cancers and not know it? (a) Yes
(b) No
(c) Don't know

7. Do you think the chances of cure for either of these cancers is (a) Good
(b) Fair
(c) Poor
(d) Don't know

SECTION F

Some illnesses prevent us leading our normal active lives. How much of an effect would the following illnesses have on your life.

Please tick the appropriate box for each illness

	Terrible effect	Large effect	Small effect	No effect
High blood pressure				
Heart attack				
Cancer				
Peptic ulcer				
Constipation				
Stroke				
Migraine				
Diabetes				

This is the last section. Please remember all your responses are strictly confidential and only your own doctor will see the answers. The information is necessary to help decide priorities for further health campaigns.

Please circle the appropriate answer as before.

Please state occupation.....
(If retired please stage last job)

Are you currently unemployed YES/NO

At what age did you leave full time education.....

Do you smoke? YES/NO

Have you ever had a previous health check-up? YES/NO

Ladies - have you ever had a cervical smear test? YES/NO

have you ever had a breast examination? YES/NO

Thank you for your co-operation. Could you now return the form in the stamped addressed envelope to the surgery?

Case-finding approach

The GP in this study initiated the screening process by inviting any individual fitting the entry criteria to participate in FOB testing, as part of a routine consultation.

Prior to the commencement of surgery, the notes were flagged with a coloured slip of paper to indicate possible eligibility by age. If the patient did not present with a GI complaint the G.P. then invited the individual to see the investigator (EMC) in a separate room to participate in the screening programme. If the patient refused, this was recorded on the card along with any reasons given for this so that an accurate account of compliance and non-compliance could be kept.

Screening Approach

This study ran subsequent to the case-finding approach and the individuals selected were invited by one of two standard letters to attend their practice surgery for a general screening check-up or a 'bowel screening' programme.

These letters, shown opposite, were typed on practice headed note paper and signed by the senior partner of the group practice. Only four practices, Meanwood, Street Lane, Burmantofts and Slaid Hill were used for this study. Burmantofts and Slaid Hill are geographically and demographically removed but share the same GP's allowing comparisons of the effect of social class and education on compliance without the bias of different GP's being involved.

Selection was based on obtaining as close a match as possible to the 'case-finding' group in terms of age, sex and

Letter from GP to the general check-up group.

Dear

as a result of a recent survey performed in the practice we have found there is a demand for some simple type of health check-up. I am writing to you therefore to offer you and many other people in your age group an invitation to take part in a Health check-up programme. The opportunity to have your blood pressure checked, your urine tested, and to be given a general information sheet about a healthy diet, will be available to you in the surgery, if you desire. At the same time some 'do-it-yourself' tests to check your tummy for problems will also be available . The check-up will be quick, no examination is required and all you have to do is make an appointment in the usual way to see Dr Chisholm, who is helping us with this programme, on a Thursday afternoon 4pm-7pm or on Sat 26th NOV or Sat 17th Dec from 8.30am-12am. This offer is only open for a strictly limited time, so please make use of it, as it is certainly to your advantage to come along.

Yours sincerely,

Dr. P. Lanfear

Letter from GP for the GI check-up.

Dear

as a result of a recent survey in the practice we have found that there is a demand for a simple check-up. I am writing to you therefore to offer you and many other people in your age group an invitation to take part in a health check-up programme. We now have available some simple tests, which you do yourself, which can detect problems in the stomach or bowels even though you feel well. People at your age are at greatest risk of developing these problems however the earlier that such problems can be found the better and more successful is the treatment for the patient. The tests don't take long to do and no examination is required. All that you need to do to take part is make an appointment in the usual way to see Dr Chisholm, who is helping us with this programme, on a THURSDAY 3.30-7PM or on Sat 26th Nov or Sat 17th Dec 8.30-12noon. This offer is only open for a strictly limited time, so please make use of it, as it is certainly to your advantage to come along.

Yours sincerely

Dr. P. Lanfear

whether or not the patient had seen their GP within the past 12 months. Further selection was also dependent on no active GI treatment or recent GI referral being found in the medical records.

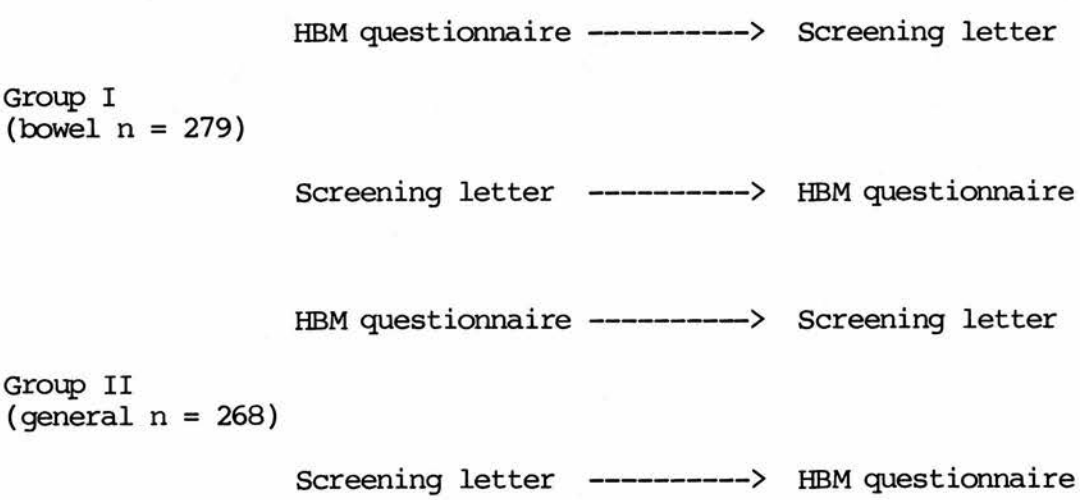
Such selection was difficult to obtain since three practices did not have age:sex registers and over 1400 records were reviewed in this process. However, the match for age and sex for the age groups 50-64 years is close.

Randomisation into the 'bowel' check-up or 'general' check-up groups was then performed by placing all National Insurance numbers ending with odd numbers into the bowel group and even to the 'general' group. However, in any given household the female spouse received the same invitation as her husband irrespective of National Insurance number.

The design of this study is shown opposite (fig 4). As illustrated one final division of these groups was performed. Half of each group was randomised to receive the HBM before the screening invitation and half was to complete the HBM on attendance for screening. This randomisation was simply performed by taking alternate names from each year of age from 50 years to 70 years.

Finally, for one week a Health Visitor was substituted for the doctor in the screening clinic to assess whether the population would express any preference as to who should perform screening.

Fig 4
Flow diagram of compliance study



Group A = HBM questionnaire before screening

Group B = Screening invite before the questionnaire

Statistical Methods

Simple comparisons between compliance and non-compliance data were analysed by the Chi square test.

As the anticipated sample size was approximately 450 individuals and the type I error was set at 0.2 and the type II error at 0.95, a 15% difference in attitudes would be required to exhibit a significant difference between compliance and non-compliance for the HBM data.

The statistical package for social sciences was used on the University of Bradford Amdahl VM 470 computer to analyse the HBM data where the Cronbach Apha coefficient of internal consistency, item analyses, analysis of covariance and discriminant analysis were performed. The programmes were preset to allow for the type I and type II errors, thus all p values attained had to show at least a 15% difference to be truly significant.

The scales were given a numerical value based on the total score gained for the responses to each question on the scale. The scores ranged from 1 to 6 for each question and were weighted to coincide with the suggested trend for the HBM. The value per individual item is shown on the HBM in the Appendix.

Results

Case-finding Study

Compliance by age, sex and general practice were all measured and are related here.

Overall Results

535 subjects were approached by their G.P. 441 (82.4%) agreed to participate and completed at least two of the tests. 405 individuals then completed and returned the FOB test they had been issued giving a 91.4% return for those accepting an FOB package and 75.7% overall for the group.

Age and compliance

The mean age for those subjects who performed at least one test was 59.3 years. The mean age for the 94 non-compliers was 64.5 years. The following table shows the distribution of those 441 individuals by age in 5 year blocks.

Table 3.2

Compliance for a single screening agent by age.

	<55yrs	55-59	60-64	65+	Total
Compliers	126	96	114	105	441
Non-compliers	14	16	30	34	94
Total	140	112	144	139	535
Percentage	90	85.7	79.2	75.6	82.4

In the following table the return of completed FOB's is shown against age and the percentage return for the whole group is calculated.

Table 3.3

FOB returns by age

	<55yrs	55-59	60-64	65+	Total
FOB returns	113	91	102	99	405
Percentage	80.7	81.25	70.8	71.2	75.7

Sex and compliance

306 women and 229 men were invited to participate in the study: 242 (79%) females and 199 (86.7%) men accepted the invitation and completed at least one test. The differences in return of the FOB packages by sex are shown in the following table.

Table 3.4

FOB returns in relation to patient's sex

	Females	Males	Chi Test
Total number	306	229	
Accept one test	242	199	5.52 $p<0.02$
Non-compliers	64	30	
FOB returned	222	183	4.16 $p<0.05$
Percentage FOB	72.5	79.9	

Twenty two women in the non-complier group were on anxiolytic agents compared to one male in the corresponding group. Seventeen of these women specifically mentioned fear of cancer and of finding a positive test and gave these reasons for failure to accept the screening offer.

Compliance by general practice

This data is summarized in the following table (Table 3.5).

Table 3.5

Compliance by general practice

	Acceptance one test	Refusal	FOB returned	Percentage FOB overall
Street Lane Professional	103	18	94	77.7
Meanwood Mixed class	148	25	136	78.6
Burmantofts Inner city	65	12	64	79
Chapeltown Inner city	54	12	46	69.6
Shaftesbury Inner city	69	27	65	67.7

No significant difference was seen for FOB return between any of the general practices.

Indirect Screening Approach

In the following table (Table 3.6) the number of patients accepting an invitation to screen is shown for each offer.

Table 3.6
To show compliance by screening offer

	Attendance		FOB return		Absolute FOB return
	No.	%	No.	%	%
General check No.= 268	138	51.4	136	98.5	50.75
GI check No.= 278	135	48.6	132	97.7	47.3

Compliance by age

The mean age of the compliant group was 58 years and for the non-compliers 58.4 years. There was no statistical difference by age for compliance between the two groups as shown in the following table.

Table 3.7 Compliance by age

	<55	55-59	60-64	65+	Total
Complier	90	84	71	28	273
Non-complier	95	72	79	28	274
Percentage	48.6	53.8	47.3	50	49.9

Compliance by sex

139 of 282 females (49.3%) and 134 of 265 males (50.6%) attended the screening appointment. No statistical difference was found between the sexes for compliance to the FOB package.

Compliance by GP practice

The results are tabulated below showing attendance by offer and by practice.

Table 3.8

Compliance per general practice

	General check		GI Check		Total	
Practice	No.	%	No.	%	No.	%
Street Lane	44	58.7	42	59.2	86	58.9
Meanwood	34	46.6	41	57.7	75	52.2
Burmantofts	29	44	17	26.5	46	35.7
Slaid Hill	34	54	32	50	66	52

The differences in attendance between the Burmantofts practice and the three remaining practices are significant using the Chi squared method ($p<0.001$, $P< 0.01$, $P<0.01$ respectively). The general practitioners for the Burmantofts and Slaid Hill practices are the same.

Further screening findings

40 of 41 individuals made appointments to see the Health Visitor when told the doctor would not be available. The remaining individual phoned again and was seen by the investigator one week later.

There were no subjects who refused to have their blood pressure recorded and 97% subjects brought a urine specimen for testing. Only three individuals in the whole study refused to give a specimen of blood, but 52 subjects refused to complete the self-administered symptom questionnaire unaided.

21 individuals were found to be hypertensive with diastolic pressures greater than 100 mmHg and were subsequently reviewed by their GP. 19 are now receiving antihypertensive therapy. 12 women who had not previously had a cervical smear test were enrolled and 4 individuals with microscopic haematuria had a normal midstream sample of urine and urinary cytology.

Results of Health Attitude Questionnaire

Pilot Study

Forty-five of 48 (94.7%) subjects in the complier group from the case-finding study completed the HBM questionnaire. By contrast only 21 of 46 (45.6%) in the non-complier group co-operated in this way.

Completion of the six health belief scales and the basic epidemiological questions was greater than 95%. However, the completion of the mood scale was less than 30% and the values achieved made the inventory valueless. The mood scale was therefore dropped from the HBM for the main study.

Reliability, as assessed by the Cronbach Alpha coefficient, was high for all scales ranging from 0.57 to 0.84 indicating acceptable levels of internal consistency.

Validity as assessed by an item analysis of the individual questions in the scales and their correlation with known screening outcome was high. Six questions in the general health scale, four in the vulnerability scale, eight in the benefits and barriers scale, six in the attitudes to illness scale, all ten in the knowledge scale, and six perceived severity scale, and the scales themselves correlated significantly with compliance outcome (range $0.02>p>0.0001$).

In view of these findings the questionnaire was unchanged with the exception of the removal of the mood scale/psychological inventory.

Main study

A. Descriptive measures

401 completed questionnaires were available for analysis at completion of the study. 252 HBM were completed by compliers to a screening invitation and 149 by non-compliers. 20 individuals attending for screening in Group B and who were seen by the Health Visitor were not required to perform the HBM and so were excluded from the analysis. A further 42 individuals who were non-compliers for the study were visited at home to invite them to discuss their failure to comply and to complete the HBM. Whilst opinions were expressed by some no further HBM were completed. Thus 443 of 527 (83%) individuals were approached to fill in a HBM questionnaire with 76% completion for the whole group.

B. Item Analysis of Questions

(i) Reliability

Internal consistency of the subscales was used assessing coefficient alpha (Cronbach, 1946).

Table 3.9

Alpha coefficients for Health Belief Scales

Scale	Coefficient alpha
General health belief	0.60425
Vulnerability	0.67410
Benefits and barriers	0.76968
Attitudes to illness	0.65261
Knowledge of cancer	0.71727
Perceived severity	0.72947

All scales showed considerable and acceptable internal consistency. Whilst internal consistency only provides one measure of reliability and ideally it would have been desirable to evaluate test/retest reliability, it was not felt possible to achieve this and proceed to screening without producing bias or causing a major delay in the study.

(ii) Interdependence of Scales

Table 3.10

Spearman Rank order correlations between Health Belief Scales

	Vuln	B & B	A/I	Know	Sev
General Health Belief (GHB)	0.07	0.514 p<0.001	0.218 p=0.001	0.379 p<0.001	0.0754
Vunerability (Vuln)		0.015	0.1201 p=0.008	0.1680 p<0.001	0.0925 p=0.032
Benefits & Barriers (B & B)			0.3506 p<0.001	0.5899 p<0.001	0.0501
Attitudes to illness (A/I)				0.3446 p<0.001	0.0964 p=0.026
Knowledge (Know)					0.0226
Severity (Sev)					

Examination of the inter-health belief correlations indicates a number of highly significant relations. This suggests that the scales are related, interactive and seem to follow the pattern proposed by Becker (1974) and Cummins et al (1978).

(iii) Relationship between measures of Health Belief Scales and Compliance (Validity)

Table 3.11

Correlation (Spearman's Rho) between Health Belief Scales and compliance

Scale	Correlation	Significance p
GHP	0.1517	<0.001
Vuln	0.1283	<0.005
B & B	0.878	=0.04
A/I	-0.0012	=0.491
Know	0.1426	<0.002
Sev	0.0770	=0.062

Four scales correlate significantly with known compliance outcome to a screening offer; the general health belief scale, vulnerability, benefits and barriers and the knowledge of cancer scales. These four scales can be said to be predictive of compliance, having been validated against an objective outcome criterion.

(iv) Item Analysis of Individual Items in Scales

(Validity)

(a) General Health Belief Items.

Table 3.12

Correlations (Spearman's Rho) between questions of GHB scale and compliance

Question		Correlation	Significance p
7	Regular medical check-ups are useless unless you are ill	0.24	<0.001
8	Good health or bad health is something you just have to put up with	0.166	<0.001
9	I think that people are fanatical about health these days	0.107	=0.017
10	Six monthly check-ups at the dentist are a waste of time	0.152	<0.002

Four questions in the general health belief section correlate strongly with compliance behaviour. Non-compliers agree more readily with the negative sentiments expressed in these statements than do compliers.

(b) Perceived Vulnerability Items

Table 3.13

Correlations (Spearman's Rho) between questions on Vulnerability Scale and compliance behaviour

Question		Correlation	Significance P
3	If I wait long enough, I will get over most illnesses myself	- 0.1733	<0.001

This scale has failed to determine major differences between compliers and non-compliers with the exception of question 3. It would appear that non-compliers accept this premise, whilst compliers do not, and that according to this scale in this HBM there is no other difference in perceived vulnerability to distinguish between the two behaviour patterns.

(c) Benefits and Barriers

Table 3.14

Correlation (Spearman's Rho) between questions on benefits and barriers and compliance behaviour

Question		Correlation	Significance p
1	There is nothing I can do to prevent illness from happening	0.13	<0.005
2.	Finding a disease early makes no difference to the success of the treatment	0.2004	<.001
3.	I am too old to worry about having health check-ups	0.264	<0.001
5.	Having a medical check-up usually stirs up trouble	0.207	<0.001
6.	I'd be frightened to have a check-up in case something was found	0.25	<0.001
7.	I'd be prepared to give up my time if I could have a free medical check up with my GP	0.27	<0.001
9.	There is no point having a check-up if you have been well all your life	0.233	<0.001
10.	Having a regular check-up for cancer is a good idea	0.16	<0.001

The findings indicate that non-compliers perceive few benefits to preventive health care whilst compliers see the advantage in cancer screening. This is similar to other HBM studies. Further the non-compliant subjects are concerned about the possible deleterious side-effects of looking for cancer.

(d) Attitudes to Illness

Table 3.15

Correlation (Spearman's Rho) between questions on Attitude to Illness scale and compliance behaviour

Question		Correlation	Significance p
4	I can never see the doctor when I want	0.1645	=0.017
6	Doctors don't listen enough to their patients	0.147	<0.002
7	Doctors should spend more time telling patients how to stay healthy	-0.19	<0.001
9	I don't like visiting hospitals	0.101	=0.022
10	I worry about having to go into hospital	0.144	<0.002

It would appear that non-compliant individuals show resentment towards health services compared to compliant subjects. In particular it would seem that non-compliers feel that there is an excessive emphasis on preventive medicine.

(e) Knowledge Items

Table 3.16

Correlation (Spearman's Rho) between knowledge of cancer and compliance behaviour

Question		Correlation	Significance p
1	You can have cancer and not know about it	0.135	<0.004
2	Finding cancer early leads to a better chance of cure	0.199	<0.001
3	Tests can detect cancer before you feel unwell	0.197	<0.001
4	No matter where you find cancer there is always a poor outcome	0.102	<0.02
5	Cancer just about always means death	0.139	<0.003
6	The treatment for cancer is worse than the disease itself	0.147	<0.002
7	Having cancer is the worst thing that can ever happen to anyone	0.145	<0.002
8	Some types of cancer can be cured more effectively than others	0.085	=0.046
9	If I had cancer I would want to be told	0.031	<0.005
10	If I thought I had cancer I would put off going to see the doctor about it	0.145	<0.002

Examination of these correlations indicates that compliant subjects are knowledgeable and positive in the value of early detection of cancer whilst non-compliers appear to believe that cancer is incurable and the treatment offered is unlikely to be of benefit.

(f) Perceived severity

Table 3.17

Correlations (Spearman's Rho) between perceived severity of items with compliance behaviour

Conditions	Correlation	Significance p
Hypertension	0.102	<0.02
Heart attack	0.124	<0.007
Cancer	0.122	<0.008
Peptic Ulcer	0.122	<0.008
Constipation	0.107	<0.02
Stroke	0.1	<0.02
Migraine	0.12	<0.009

From these results it would seem that for most non-compliers any disease but particularly cancer, peptic ulcer and heart attack will produce a major effect upon their life style compared to the effects these diseases would be felt to have on the complier group. For some reason migraine, also appears to be seen as a more serious condition to have compared to a stroke.

V. Summary

Examination of these results confirms an acceptable reliability of the scales as determined by internal consistency. Correlations between scales and an objective measure of outcome suggests the questionnaire offers valid measures. The use of an item analysis has indicated some items of predictive value for each scale: a total of 35 of 58 items in the six HBM scales were found to be predictive for outcome in response to a screening invitation.

C. Univariate analysis

Examination of the findings after univariate analyses indicates that 5 variables can independently differentiate compliers from non-compliers: general health beliefs, benefits and barriers; attitude to illness; knowledge of cancer and further education.

Whilst the series of univariate analyses of variance indicate differentiating variables for compliance behaviour, they make no allowance for complex inter-relationships that may occur between variables. Thus, the use of a multivariate technique rather than a set of univariate analyses should elucidate any interaction between variables.

(b) Multivariate Analyses (Discriminant function analyses)

However, as the above analysis defines variables which independently discriminate between compliance groups, then making allowance for complex inter-relationships by a multivariate method, is likely to increase prediction of outcome.

Table 3.18

Standardised Canonical Discriminant Function Coefficients after Step 9

Variable	Function
Vulnerability	- 0.28345
Benefits Barriers	0.67918
Knowledge	0.25528
Feelings	0.17154
Personal Contact	0.26135
Cure	- 0.352
Employment	- 0.15
Educucation	- 0.28
Smoking	0.22

An interaction of the above 9 variables significantly discriminates between the two compliance groups.

$F = 5.1215$

$p < 0.0000$

Canonical correlation = 0.3714376

Used to predict group membership for the 401 individuals in the study, the overall classification rate was 67%. The detailed breakdown is shown in the two following tables.

Table 3.19

Canonical discriminant functions evaluated at group means:

(Group centroids)

Group	Function
Compliers	- 0.30931
Non-compliers	0.51482

Table 3.20

Classification of results using group discriminant functions

Actual Group	No. cases	Predicted Group Membership	
		1	2
Compliers 1	252	182	70
		(72.2%)	(27.8%)
Non-compliers 2	149	60	89
		(40.3%)	(50.7%)

The overall prediction in terms of group membership is 67%

Discussion

Whilst there have been numerous studies to determine the value of the faecal occult blood test in the detection of asymptomatic colorectal neoplasia, few investigators have assessed the factors influencing the population's compliance for FOB testing while screening for bowel cancer. Since the cost-effectiveness of any such screening program is dependent not only on the validity of the test agent but also on compliance for that test, then the low acceptance of the direct postal FOB method (36% on average in the UK) will not permit colorectal cancer screening to be viable. These low compliance levels were the stimulus for the author to examine alternative approaches to the promotion of colorectal cancer screening utilising the primary health care facilities already available.

The results of the case finding study with a direct approach from the GP would seem to bear out Farrand's views (Farrands et al,1981 and 1984a) that the general practitioner should have a greater role in promoting bowel cancer screening. Our 75% return rate from a relatively random population would render population screening with FOB testing a more feasible exercise than could have hitherto been anticipated. Further as shown in Table 3.5 the results are not heavily biased by the inclusion of a preponderance of middle class individuals, a criticism leveled at the original pilot study performed by Professor Hardcastle and his colleagues (Hardcastle et al,1981) by Million's group (Million et al,1982). A 71% return in the working class group for this study represents a potential step forward in

the response of this particular group for screening activity especially as these inner city practices have serious social problems and have a crime rate third only to Toxteth and Brixton.

Unlike previous studies (Hardcastle et al,1983; Lallemand et al,1984; Nichols et al,1986), it was found that men had a higher response to screening than women. Farrands et al (1984a) also noted that the compliance of men for FOB testing was increased and greater than for women following an interview. It may be that men are less likely to respond to a screening invitation than women without some form of personal reinforcement.

The explanation for the very high response rates for the direct invitation is not clear since the reasons for acceptance were not adequately recorded at the time. However several factors could be proposed as being relevant; the simplest would be embarrassment at refusing the GP having just consulted him; or the GP is seen as someone responsible for the health of the individual and so the offer to screen must be valid; the practice surgery is less threatening and impersonal than a screening clinic (French et al,1982); and finally it is possible to discuss and make a more objective decision regarding screening in general and FOB testing in particular if direct contact is available.

It would certainly seem that the enthusiasm of the general practioner and the screening facilitator is vitally important to the success of this type of "opportunist" approach to screening. Nichols et al (1986) have shown similar results to this study using exactly the same approach from the GP to initiate screening and found that the compliance rates varied considerably within the

practices depending on which GP was promoting the screening. In the current study several GP's within the practices did not wish to be involved at all or rarely referred individuals for counselling. In a separate study Nichols et al (1986a) showed considerable variance in the attitudes of GP's to the merit or demerit to colorectal cancer screening and similarly Dent et al (1978) found poor knowledge of "risk" lesions for colorectal cancer and negative attitudes to screening with FOB testing in the medical profession. As suggested by Nichols and her colleagues (1986a) this aspect of screening promotion cannot be ignored if a GP lead screening service is to be successful.

During this study it was established that the apparent 'normal' referral rate to a GP for 1900 individuals aged 50-70 years was 78% patients attended the surgery at least once per annum. This is comparable with other published GP data on referral practice (Andersen,1977; Nichols et al,1986). The referral patterns for the case-finding and screening group are similar to the 'norm' and therefore it is felt that these groups are comparable and fairly representative of this particular population under study and are not subject to any large selection bias. This should therefore enable valid comparisons to be made between each group in this study and other screening studies.

It would therefore seem that the results of the current 'screening' study support the contention that the GP is seen as someone representing health care and that the possibility of discussing the need for screening has influenced screening uptake. This support is in 2 parts; 50% responded to the letter of

invitation and attended the practice for screening compared to 36% complying with direct postal FOB's in other studies. Secondly, there was no difference in compliance for either screening offer. This would suggest that the increased compliance was due to the letter coming from the GP and that the surgery was seen as the appropriate setting for health activity. This finding has also been noted for breast cancer studies and colorectal cancer programmes (Hobbs et al,1980; Edinburgh Breast Screening Clinic, 1978; Hardcastle et al, 1983). Nichols et al (1986) have also shown an increase in response to a specific appointment for screening in the GP surgery with 49% compliance compared to a 38% response to a postal method.

Once these individuals were enrolled by whatever method the return of completed FOB's was greater than 90%. This, by implication, suggests that the test can be completed readily in a population sufficiently motivated. However the way FOB screening is currently packaged that motivation is not enough to overcome a natural distaste for stool testing. Silman and Mitchell (1984) have also reported similar findings.

There are several implications for the cost-effectiveness of screening using these approaches, accepting that there are limitations imposed by the small numbers employed in this study. Whilst direct postal FOB screening is simple and easy to organise, little account is made of the 50%-70% FOB's lost from the programme by non-return. Since the bulk of the costs are made up by these kits, estimated to be 10 - 20 times the cost of postage, this is clearly a severe limitation to the effectiveness of

screening. With the 'case-finding' or 'screening' approach employed in this study, these losses do not occur. In the 'case-finding' approach the initial letter of invitation is not required further reducing costs. Compliance in each study was significantly increased compared to previous postal only screening methods (Chi square 21.4, $p < 0.001$) and was achieved with little extra input (Table 3.1). It would have been most interesting to have repeated Lallemand et al's (1984) approach of reminder letters to see if further encouragement from the medical promoters would have increased the compliance rate. Unfortunately the general practitioners were keen for their patients not to be pressured into acceptance of screening and this avenue was not pursued.

Table 3.8 shows a disparity in compliance by social class for the screening approach in this study. Low compliance in the lower socioeconomic groups for cervical and breast cancer screening programmes has also been noted (Cardiff Cervical Cytology Study, 1982; Wakefield and Sansom, 1966). Farrands et al (1984) have not found that social class is a significant factor determining compliance for FOB testing. The table suggests that, despite the small numbers, the best return for investment may be direct postal promotion for upper social class areas with direct input from the GP for the lower social class. This is worthy of further investigation by cost-analysis in a large controlled study.

The data table 3.8 is disturbing as it demonstrates 40% of the professional group did not respond to the screening

invitation. Such individuals should belong, theoretically, to the most accessible and knowledgeable group for a preventive medicine campaign. The health belief questionnaire may explain why such individuals do not comply for screening.

It was surprising that such a high response to the questionnaire was achieved given the abstact nature of the questions. The HBM not only recorded the attitudes of the screening population but highlighted significant differences in these responses for compliers and non-compliers in 35 items from the 6 scales. In addition differences in a further 5 demographic items were noted. However as demonstrated by Antonovsky and Anson (1976) and by Stillman (1977) single responses to questionnaires indicating good awareness of the value of screening for breast cancer do not directly correlate with screening outcome. Similarly Farrands et al (1984a) found that 75% subjects in their study felt check-ups were important but only 50% complied for FOB testing.

The use of discriminant analysis has shown the interaction of the 6 scales and may indicate the balance between the perceived advantages and disadvantages of health activity held by other factors such as resentment of medical practitioners or how susceptible one feels to developing the disease in question (Table 3.21). Thus an individual who has exhibited high benefit and knowledge scores may not attend if he does not feel at risk of harbouring cancer. These findings support Becker's proposal that making health decisions is a dynamic process of multiple interactive factors the sum of which decides the final action (Becker, 1974). Silman and Mitchell (1984) also noted that their

Table 3.21

Attitude profiles in a screening population

Compliance	Non-compliance
High cancer knowledge	low cancer knowledge
Low vulnerability	high vulnerability
High benefits to screening	low benefits
Realistic attitudes to illness	unrealistic attitudes
Respect for doctors	poor respect for doctors

non-complier group for FOB testing did not appreciate that they were at risk for colorectal cancer. This was especially disappointing for Silman and Mitchell as their study included a high intensity educational programme to highlight the risk of the individual for colorectal cancer.

Whilst French and her colleagues (1982) did not use the HBM in their study of attitudes to breast cancer screening they did find that there were several factors common to non-compliers. These included feelings of vulnerability, pessimism towards the value of early detection of cancer and fear of disruption to their lives. This appears to correlate well with the current study and may indicate some fundamental attitudinal problem to cancer screening that will need to be overcome if such screening is to be viable.

The approach used in this study has differed from previous reports. Unlike Farrands et al (1984a) no input from a medical representative was present before the HBM was completed thus reducing any potential bias that could be introduced by an interviewer (Collen et al, 1969). Both compliers' and non-compliers' attitudes were recorded unlike Halper et al (1980) who looked at healthy volunteers for sigmoidoscopy but who refused FOB testing and from Silman and Mitchell (1984) who failed to examine the compliers for their study. Thus both sets of workers were unable to compare the compliers with non-compliers for FOB screening in the population at large for true differences in attitudes to screening with FOB tests. The advantages for this approach are that the only external influence on an individual's

responses to the questionnaire and to the screening offer could be from immediate family or friends who might normally help in health decision processes. The disadvantage is that the attitudes of 25% of the non-compliers are not available to the investigator. However a considerable number of the non-compliers were approached at home but still refused to discuss the matter indicating that such data may never be readily available. This difficulty has also been noted by other workers (Cummins et al,1977; Eraker et al,1984) although Farrands et al (1984a) did not apparently experience these difficulties.

It is quite remarkable however that 149 individuals who failed to attend for screening should complete a 71-item questionnaire with difficult abstract ideas at all. Clearly an understanding of this groups' attitudes exhibiting compliance to some requests from the medical profession could increase the potential recruitment of these individuals for future screening programmes. It is conceivable that these individuals made up the extra 25% compliant individuals in the direct approach from the GP during a consultation and that a more personal approach is required to trigger a positive screening response.

The cost in time and expense to the GP to institute his own case-finding or screening studies would not be great. The GP's were not burdened by any extra work or prolonged consultations to promote the screening. In this study, whilst the patient was requested by the GP to see a medically qualified researcher, our Health Visitor seemed acceptable to the public. Other studies have successfully used Health Visitors (Million et al, 1982) or

practice nurses (Cullum and Savory, 1983; Grace, 1983) to carry out screening, although Nichols et al (1986) felt that the use of an ancillary worker lead to a reduced uptake of FOB screening. Grace (1983) has also detailed how a group practice can efficiently and cost-effectively run a screening programme without increasing demands on the GP's time or money. A more recent report from Fullard, Fowler and Gray (1987) has emphasised the need to utilise the practice nurses for preventive health measures and thus maximise the return of the primary health care resources. It is particularly gratifying for the author that the screening clinic he initiated in one of the group practices is still on-going. It is thus envisaged that for urban group practices with an attached Health Visitor or practice nurse, screening for common diseases including colorectal cancer could be viable.

It may be concluded that the reluctance of the general public to perform stool testing can be overcome by adequate promotion and explanation by the medical profession. Furthermore, the GP is ideally placed to take the lead in promoting colorectal cancer screening in the community. Finally, there are two distinct attitude profiles which determine compliance to screening measures. There is a need for continued research to understand the factors influencing compliance for colorectal screening in order that such screening can become a valid proposition in the United Kingdom.

Chapter 4

Early detection of Colorectal and Gastric cancer in a symptomatic population.

Introduction

In chapter 2, it has been shown that there is a high prevalence of upper and lower GI symptoms within the general population during a given time. The fact that 38 individuals with symptoms were investigated and no neoplastic condition identified serves to emphasise that symptoms merely reflect organ dysfunction and not a particular pathological process.

This places the GP in a difficult position if the symptoms he elicits from his patients are poor indicants of cancer or other serious GI conditions. No GP will wish to miss a possible diagnosis of cancer and he is constantly under pressure from his hospital colleagues when he reads that there are considerable delays in the diagnosis of cancer at the practice level (MacAdam, 1979; Holliday and Hardcastle, 1980; MacArthur and Smith, 1984); yet at the same time he is told that he cannot have open-access to endoscopy as he will overwhelm the available facilities (Mann et al, 1983).

In view of the findings in chapter 2, there is clearly a need to further define 'risk' of cancer from within a symptomatic poulation. Selective screening of epidemiologically defined high risk groups is of course important but as pointed out by Schottenfeld (1975) less than 10% of the cancer pool is thus identified. However indiscriminate unselective screening is expensive and ineffective. Thus if one suspects that new-onset dyspepsia is a good indicator of gastric cancer risk (Gear and Barnes, 1980) then the yield for cancer on endoscopy is 2.4% (Allum et al, 1986). Such a yield is probably untenable in a

screening programme. Read et al (1982) have shown that the pick-up rate of gastric cancer is 1.4% of all gastroscopies performed and the number of normal gastroscopies performed may be as high as 80% (table 1.6). Similarly, Leicester et al (1983) and Farrands et al (1985) are looking to reduce the number of unnecessary barium enema examinations performed to exclude colorectal neoplasia.

Recently, two separate approaches to defining the risk for specific disease processes have been investigated. These are the analysis of symptom clusters to define the presence of peptic disease and en passant gastric cancer and an appraisal of the interaction of several tumour markers to detect GI cancer preoperatively.

The statistical analysis of symptom complexes has been pioneered by Professor Wilfred Card (1967) to predict the relative risk of a particular disease using likelihood ratios. His successors have pursued this theme to produce the 'Gladys' system to define the probability of a patient with dyspeptic symptoms having a peptic ulcer (Spiegelhalter, 1985). In Leeds, De Dombal has described his system of computer aided diagnosis as an aid to the diagnosis of acute abdominal pain (De Dombal et al,1972) and for analysis of "dyspeptic" symptoms (Horrocks and De Dombal, 1975, 1978). Recently Mann et al (1983) have reported their experience with multivariate analysis to predict the risk of an individual with upper GI symptoms of harbouring either peptic ulceration, peptic stricture or gastric cancer. Using an initial database of 235 subjects they analysed the responses to a 27-item questionnaire and produced a scoring system which was then applied

prospectively to a further 356 patients. The system identified 98.7% of patients with the above three conditions whilst in theory it could have reduced the number of endoscopies by 30%.

A second approach has been a renewed interest in the use of serum tumour markers to identify cancer preoperatively. Initially it was hoped that a serum tumour marker, such as carcinoembryonic antigen (CEA), would have sufficient sensitivity and specificity to detect GI cancer preoperatively in a symptomatic individual. The recent National Institute of Health Concensus Report (1981) declared that CEA should not be used as a preoperative investigative tool to detect GI malignancy and no other individual tumour marker has been found to be of value. However, the investigation of combinations of CEA and APRP's has shown that they may aid in prognosis for both gastric (Rashid et al, 1982) and colorectal cancer (Ward et al, 1977). This observation stimulated Chu and colleagues (1982) to assess the combination of CEA and AGP preoperatively in patients with colorectal cancer, where the sensitivity for detection of cancer increased significantly but was associated with a reduction in specificity. De Mello et al (1983) pursued this approach by using a panel of six non-specific biochemical markers to define 'cancer risk' preoperatively; by applying multivariate analysis they identified 162 GI cancers (81%) with a false positive rate of 16%. Furthermore, Walker and Gray (1983), applying discriminant analysis to a battery of markers found that the combination of serum protein hexose and CEA could significantly increase the detection preoperatively of colorectal cancer.

It was the work of Mann et al (1983) and De Mello et al (1983) that stimulated the following investigations to define the probability of colorectal and gastric cancer being present in a symptomatic individual.

Aims

(1) To examine the use of a panel of tumour markers to detect GI cancer preoperatively.

(2) To determine the value of multivariate analysis to predict risk of cancer in a symptomatic population using either tumour markers, symptoms or a combination of both as indicants of risk.

(3) To compare the multivariate approach to that of likelihood ratios to determine risk of cancer.

(4) To develop a symptom scoring index of risk for gastric cancer for use in a prospective study in a dyspepsia clinic.

Methods

Patients

86 subjects with GI cancer, 168 with benign GI disease and 720 individuals from the general public were investigated. Of the 86 GI cancers, 57 were colorectal, three of which were Dukes' stage A, 14 Dukes' stage B, 23 Dukes' stage C and 17 Dukes' stage D. The remaining 29 cancers were all gastric, three stage II, 13 stage III and 13 stage IV.

The benign group comprised individuals referred from one general surgical clinic for upper and lower GI endoscopy and encompassed the common conditions of peptic ulcer disease, gastritis, diverticular disease, irritable bowel and inflammatory bowel disease.

The 720 "normal" individuals were recruited from the screening study and therefore were aged between 50-70 years old and felt to be free of overt active GI disease. These individuals were included since it has been shown by Jones (1976) and Thomson and Heaton (1980) that many apparently normal individuals may have present, at any given time, symptoms suggestive of significant gastrointestinal disease. Thus to generate a system to determine the risk of cancer in an individual it is necessary to take account of the background prevalence of symptoms within an age-matched "normal" population.

All subjects completed a self-administered questionnaire and gave a blood sample for the estimation of four serum tumour markers.

Questionnaire

The 41-item questionnaire as used in the previous chapter was supplied to all symptomatic patients for completion. All subjects attending for endoscopy were given the form to complete by the endoscopy nurse and inpatients were approached by the investigator.

Tumour markers

4 serum tumour markers, carcinoembryonic antigen (CEA), alpha-1-acid glycoprotein (AGP), C-Reactive protein (CRP) and gamma glutamyl transpeptidase (GGT) were measured.

All patients had 10 mls of blood taken from the antecubital fossa and the sample was placed in a plain tube and allowed to clot. The specimen was then spun at 3,000 rpm for 10 minutes and the serum removed. All specimens were stored at $-20^{o}C$ until required for analysis.

Carcinoembryonic Antigen (CEA)

CEA has been assayed by a radioimmunoassay technique. A brief summary of this technique is now included. A direct radioimmunoassay method is utilized using paper discs as the solid phase. During a first incubation anti-CEA antibodies, covalently coupled to the paper disc, react with the patient sample. After washing, a fixed amount of ^{125}I labelled anti-CEA antibodies is added. During a second incubation, the added antibodies form a specific complex with the CEA molecules which are bound to the antibodies on the paper discs. The radioactivity of this complex is then measured in a gamma counter. The greater the amount of isotope which is bound, the more CEA is present in the sample.

Reagents: Supplied by Pharmacia Diagnosis AB, Uppsala, Sweden.

10 ml vials

1. Anti-CEA antibodies ^{125}I lyophilized (raised in rabbits)
   contains 1 ug-7.5 uci at the date of manufacture,
   colour coded blue - 1 vial
2. CEA-free diluent, lyophilized (pig serum) - 3 vials
3. Tween solution in 5 ml vials - 1 vial
4. CEA-standards predispensed in pig serum to
   2.5, 15, 50, 150, 500 ng/ml - 5 vials
5. CEA control serum, lyophilized - 2 x 3 vials
   in cassettes:
6. 3 x 30 anti-CEA antibody discs, in buffer solution
   (antibodies raised in sheep) - 3 cassettes

Preparation of Reagents:

(a) CEA Control Serum

The CEA control sera were reconstituted by adding 500 ul of redistilled water to each vial and allowed to stand for one minute.

(b) CEA Standard Solution

CEA standards were reconstituted by adding 1000 ul of redistilled water to each vial and left to stand for 1 minute.

(c) CEA Free diluent

Reconstituted by adding 8 ml of redistilled water to each vial and left to stand for 1 minute.

(d) Anti-CEA ^{125}I Solution

Reconstituted by adding the entire Tween solution (5 ml) to the vial.

(e) Anti-CEA Antibody Discs Ready for use

Preparation of standard curve

A standard curve was automatically prepared on every test occasion and each standard was run in duplicate and recorded using a silent 700, Electronic Data Terminal obtained from Texas Instruments Ltd., Bedford, England.

Test Procedure

Plastic test tubes with round bottoms and an inner diameter of 12 mm, were used for the test procedure (obtained from L.I.P. Equipment and Service Ltd., Shipley, W. Yorkshire).

Determinations were performed in duplicate and a standard curve was run at each test occasion.

1. One anti-CEA antibody disc, handled by a pair of forceps, was added to the bottom of each tube, except for tubes 1 and 2 (total activity tubes).
2. 100 ul of standard 2.5, 15, 50, 150, 500 ng/ml was pippetted onto the discs in tubes 3-12 and a further quality control of two previously measured specimens, one high and one low were also included in each CEA run.
3. Serum samples were diluted 1:5, mixing 50 ul of the original samples with 200 ul CEA-free diluent unless values above 250 ng/ml were expected. In such cases samples were diluted at least 10-fold (= 1 + 9), e.g. 50 ul of the original serum mixed with 450 ul of CEA-free diluent.
4. 100 ul of unknowns were pipetted onto the discs in tubes 13 and above. The tubes were covered with plastic films and agitated vigorously for 3 hours using a model R 100 Rotatest shaker (Luckham Ltd., Sussex, England) at room

temperature.

5. Each of the test tubes had all liquid removed by a vacuum pump. 2.5 ml 0.9% saline was added to all test tubes from number 3 onwards and the tubes allowed to stand for 10 minutes and removed as specified above. Thereafter, the washing procedure was repeated twice.

6. 50 ul of anti-CEA antibody ^{125}I solution was pipetted onto the bottom of all tubes including 1 and 2. Tubes 1 and 2, which contained only anti-CEA antibody ^{125}I, were used to determine the total activity added. The tubes were covered with plastic films and left to stand overnight (16-20 hours) at room temperature.

7. The liquid was removed and washed 3 times according to step 5.

8. The bound radioactivity was determined in all tubes using a gamma-counter (1270 Rackgamma II counter - L.K.B. Instruments Ltd., Selsdom, South Croydon, England).

Calculation of Results:

1. Linear interpolation: The curve relating the counting response (e.g. count rate, per cent bound, etc.) and the concentration of the standards is assumed to be made up of a series of straight lines forming the standard points. When an unknown sample is measured, the dose is obtained by linear interpolation between the standard curve points either side of the unknown . Between two standard points the straight line is assumed

to have the form:

$$\text{concentration} = ao + a1 \times \text{counting response}$$

(ao and a1 are constants)

As both R1C1 and R2C2 are points on one straight line

$$\text{and } C1 = ao + a1R1$$

$$C2 = ao + a1R2$$

$$\text{therefore } ao = \frac{C1R2 - C2R1}{R2 - R1}$$

For an unknown with response Ru (lying between the values R1 and R2) and concentrate on Cu, the concentration Cu is given by

$$Cu = \frac{C1R2 - C2R1 + C2Ru - C1Ru}{R2 - R1}$$

The relationship between the count response and the concentration of standards is expressed by:

$$(CPM - NSB) \;/\; (CPM_{REF} - NSB)$$

In this instance when the reference sample is the zero sample (the sample having a zero concentration of unlabelled standard), division on the unknown or standard count rate by this value, gives fraction bound, non-specific bound (NSB) is only subtracted when required. The form of this relationship is non-linear.

The calculation of the concentration of an unknown sample is done instantaneously so that the unknown concentration is printed on the same line after the count results.

In particular a standard curve is printed on which the values of the actual standards are printed in the appropriate

position; the scales for the plot are automatically set as the basis for interpolation. The standard curve plot allows the user to check the form of the standard curve, and if necessary, to draw in the curve to check individual values. It also allows a check to be made of individual duplicate or triplicate values, if for some reason they do not appear to follow the correct curve, the assay can be quickly recounted omitting any which do not appear satisfactory.

C-Reactive Protein (CRP) and Alpha-1-Acid Glycoprotein (AGP).

These agents were measured using a standard radial immunodiffusion technique (RID). A description of the standard technique is now presented.

The principle of RID is based on the fact that any specific antigen (e.g. serum protein) will form a precipitin complex with its specific antiserum at a constant ratio of antigen to antibody. An antigen when applied to a well in an agar substrate containing specific antiserum, will diffuse radially through the agar until the optimal rates of antigen to antibody is achieved. Thus the quantification of the protein is obtained by comparing the diameter produced by the serum protein with the diameter of the precipitation rings produced by standard commercially available serum solutions with known protein concentrations.

There are basically 2 methods of RID:

(1) The Mancini-Heremans Technique (1965) which is based on the analysis of the results after the end-point of immunodiffusion has

occurred and;

(2) The Fahey-McKelvey Technique (1965) which is designed for early read out of results.

The first technique was used which may provide more accurate results at the expense of prolonged diffusion time.

CRP and AGP

Procedure

During the preparation of the RID plates, 300 ul of the AGP antiserum (Gehring) or 120 ul of the CRP antiserum (Behring) was applied to the plate. Subsequently, the test sera and the standard sera are applied to the plates. The AGP sera require to be diluted to 1 in 11 whilst the standards are diluted to 1/3, 1/6, 1/12, 1/24. For CRP no dilution of the test sera is required whilst the controls are neat, 1/2, 1/4 and 1/8.

The plate is then stored in a horizontal position at room temperature in an airtight box and kept humid with damp tissues. The antigens are then allowed to diffuse for 48-72 hrs AGP plates may be read directly as the rings are very distinct. However, staining of the CRP plates is required to enable accurate delineation of the maximum extent of the precipitation rings.

Analysis

After the appropriate incubation time, the diameter of the precipitating rings are measured to the nearest 0.1mm in the Mancini' technique. The protein to be assayed is allowed to diffuse until all free protein molecules have reacted with the antiserum and no further extension of the precipitating rings occurs. The various proteins are characterised by different

diffusion times, at which time the end point is reached. The diffusion time depends on the protein concentration as well as the molecular weight.

Reagents

1. Barbiturate Buffer pH 8.6

Sodium diethyl barbiturate (Sodium Barbitone) 20.6 g, made up to 1 litre with distilled water (0.1M solution) and 148 ml 0.1M HCl is then added. The pH is adjusted to exactly pH 8.6 with 0.1M HCl or NaOH using a pH meter. The solution is then kept at $4^{o}C$ for further use.

2. Agarose for Skinning (2.5%)

1.25g of Agarose type II (Sigma Chemical Company, St. Louis, U.S.A.) is added to 50ml of distilled water and autoclaved to $150^{o}C$ (Instrument Steriliser, Baird and Tatlock Ltd., London).

3. Agarose for Gel

1% Agarose type II in 25% dilution of the barbiturate buffer or 1% Agarose plus 3%. PEG (polyethylene glycol 6000, BDH Chemicals Ltd., Poole, England) in buffer was prepared as follows:

Agarose - 2g + buffer 50ml + distilled water 150ml or plus PEG 6g were mixed together and autoclaved.

1% sodium aside was added as preservative.

The plates were skinned and left to dry at room temperature.

For one plate 10cm x 10cm, 15ml of agarose was required, plus the appropriate amount of antiserum, mixed thoroughly before the plate was poured. PEG is added to enhance the precipitation reaction.

Application of Sera

Forty-nine holes of 2.5mm in diameter were punched in each plate. 5ul of serum was applied to each well using a micropipette (5ul Micro/pettor 1055A Scientific Manufacturing Industries, Emerryville, California, U.S.A.). The sera were diluted appropriately, according to the protein being measured, using a Clinicon Diluter (L.K.B. Instruments, South Croydon, England).

Standards and quality control sera were also applied to the plate and diluted accordingly.

The plates were then left in a sealed container for 48-72 hours, until they had run to completion (AGP for 48 hours, CRP for 72 hours). The CRP plates were then dried and stained up in Coomassie blue, until the circles were sufficiently visible to read.

Drying and Staining Plates

1. The plates were covered with a film of distilled water and then with a layer of filter paper and dried for 15-20 minutes using many layers of tissue paper, which were continually replaced. A small amount of pressure equivalent to 1-2kg was applied on a glass plate on top of tissue paper.
2. The plates were then washed in 0.9% saline solution (20 mins - 1 hour) and the drying procedure repeated. The plates were then dried down completely using a hairdryer and stained.

The staining solution was prepared mixing up 1g of Coomassie blue, 90ml of ethanol, 20ml of glacial acetic acid and 90ml of distilled water. After staining for nearly 5 minutes, the plates were allowed to destain for a variable period of time until

they had reached the optimal point of clearness to read, using the following solution:

500ml of ethanol + 200ml of glacial acetic acid + 900ml of distilled water.

Calculation of Results

The diameters were read using a graduated eyepiece (Peak Scale LUPE 7X, Gibco Bio-Cult Ltd., Paisley, Scotland). The concentrations of proteins in each serum sample were calculated with the diameters using the Hewlett-Packard calculator and appropriate programme (Hewlett-Packard, Series 98, Model 10 Calculator, Packard Instruments Ltd., Caversham, Berkshire, England) and the results recorded using a Data Dynamics 390 Recorder (Data Dynamics Ltd., Hayes, Middlesex, England).

Gamma Glutamyl Transpeptidase

This enzyme was measured using an automated procedure as described by Haesen et al (1972).

This method utilises the action of the enzyme in converting amino acids or peptides into gamma glutamyl peptide which in the living tissue can then cross cell membranes. In the procedure any enzyme in the serum added to the system will catalyse the reaction ->

gamma glutamyl-p-nitroanalide + glycolyglycine -GGT-> gamma glutamyl glycylglycine and P-nitroaniline

P-nitroaniline can then be measured by colorimetry (wavelength 410 nm). The enzyme level can then be measured as the amount of enzyme (units/litre) that converts 1 umol of substrate (gamma glutamyl p-nitronuclide) per minute under the conditions described below.

Reagents

1. Amnediol buffer 0.05 M, pH 8.5. Chemical Composition:
   amnediol (2-amino-2-methyl-propanediol 1-3)
   distilled water.
   wetting agent Triton X-405
   Preparation. Amnediol 5.26 g (B.D.H. Chemicals Ltd., Poole, England) is dissolved in about 700 ml distilled water. The pH of the solution was adjusted to 8.7 $\pm$ 0.1 with HCl (about 25 ml is usually required). The solution is then diluted to 1000 ml. 3 drops of the wetting agent, Triton X-405 (Sigma Chemical Company, St. Louis, U.S.A.) were added and mixed.

2. GT substrate. Chemical composition:
   L-gamma-glutamyl-p-nitroanilide 2.9 mM
   Glycylglycine 22.0 mM
   Amnediol buffer 0.05 M pH 8.7
   Preparation. L-gamma-glutamyl-p-nitroanilide, 500 mg (Sigma Chemical Company, St. Louis, U.S.A.) and glycyglycine, 1745 mg (BDH Chemicals Ltd., Poole, England) are dissolved with mechanical or magnetic bar stirring in 600 ml amnediol buffer at 50-60^{o}C. The solution is stored at - 20^{o}C. Before use the solution is thawed in a water bath at 37^{o}C. It is advisable, to shake occasionally, until the substrate is completely redissolved. The pH of the solution is 8.2 $\pm$ 0.1.

3. Stock standard p-nitroaniline, 0.735 mM 101.5 mg of p-nitroaniline (BDH, Poole, England) was dissolved in 1000

ml aminediol buffer solution.

4. Diluted standards. 100 ml quantities were prepared by diluting 50, 25, 10, 5, 2 and 0.5 ml of the stock standard with buffer solution to give p-nitroaniline standard equivalent to 0.368, 0.184, 0.074, 0.037, 0.015 and 0.004 mM respectively.

5. Enzyme standard. A single point standardization was carried out with an analyzed frozen (-20°C) serum pool, dispensed in amounts sufficient for daily work.

6. Water. Distilled water, containing 5 ml 8% Brij-35 (Sigma Chemical Company, St. Louis, USA) per litre, for the wash receptable line.

PROCEDURE

The automated procedure was carried out by the Technicon Auto-analyzer ZZII (Technicon Ltd., Basingstoke, Hampshire, England). The incubation time is about 13 mins.

The calibration curves were constructed by introducing p-nitroaniline standards directly into the dialyzer by a suitable glass tube, making use of proportioning pump suction.

Statistical Analyses

A preliminary analysis of the relative frequency of positive responses to each GI question was performed using a Chi squared test to detect significantly different response rates for cancer patients compared to the remaining groups. Similarly, the cumulative frequency distribution of each biochemical variable was plotted and, by using the 95th percentile value of the benign group as a cut off point, the sensitivity and specificity of each marker to detect cancer were determined.

A comparison of three approaches was next performed. The simple combination of tumour markers has been performed as suggested by Chu et al (1981) and De Mello et al (1983). The more sophisticated approach of multivariate analysis and the use of log likelihood ratios (Spiegelhalter 1985) are then used and compared.

Multivariate Analysis

A logistic discriminant analysis (Anderson, 1972; Albert, 1982) has been employed in this study to determine which variables are significant in discriminating between the cancer and non-cancer subjects. A stepwise procedure was adopted in which variables (4 tumour markers and 18 GI questions) are added to the model sequentially and at each step the statistical significance for each term not already in the model is calculated. The most significant variable at each step is added and when no variable is significant at the 5% level the process stops. Biochemical measurements underwent a logarithmic transformation (log 10) and positive responses to the questionnaire were accorded a score of +1 and a negative response -1. Sex was coded as +1 for male and

-1 for female. The analysis was performed using the statistical package BMDP81, subroutine PLR, on the University of Leeds AMDAHL 470 computer.

To fit the model we used 54 cancer cases and the non-cancer group comprised 80 benign and 200 control population (initial data set). As more cases were enrolled it was hoped that the model could be applied prospectively, thus permitting a more accurate impression of its validity in a clinical setting (Second data set).

Log likelihood Ratios

A shortened description of this approach with a worked example follows:

For a fuller description the reader is directed to Spiegelhalter (1985). The aim of this approach is to devise a simple scoring system which will identify risk of cancer and would require only the use of a pocket calculator.

By using the same patient data set as utilised for the multivariate analysis, a direct comparison of the results from the two methods could be achieved.

(1). 'Independence' has been assumed within the diseases by using the 'Naive Bayes' model.

Denoted as:

$$\frac{P(D/S1,S2,.....Sx)}{P(\underline{D}/S1,S2,.....Sx)} = \frac{P(S1/D) \times P(S2/D) \times P(Sx/D) \times P(D)}{P(S1/\underline{D}) \quad P(S2/\underline{D}) \quad P(Sx/\underline{D}) \quad P(\underline{D})}$$

where P symptoms are shown as S1, S2, ... Sx.

the proportion of patients who have the symptom and the disease are shown as P(S/D).

the proportion of patients who have the symptom but do not have disease are shown as $P(S/\underline{D})$.

As it is easier to add than multiply, transform the formula using Natural Logarithms ($\log_e$).

To derive the 'scores' the log (likelihood ratio) has been multiplied by 5, and rounded to the nearest whole number.

Denoted as:-

$$5\log_e \frac{P(D/S1,S2,..Sx)}{P(\underline{D}/S1,S2,...Sx)} = W(S1/D) + W(S2/D) +.+ W(Sx/D\ 5\log_e P(D)$$

Where the $\log_e$(likelihood ratio) which is also known as the 'Weight of Evidence', is shown as W(S/D).

(2). The 'Initial odds' on CA were taken as the incidence rate of 4 per 1000 population > the age of 45.

(3). Thus the final $\log_e$ (odds) is achieved by adding up the relevant 'weights of evidence', and then adding on the Initial $\log_e$(odds).

(4). To turn the resulting 'final score' into its theoretical probability for disease (CA) we apply the equation:-

Score = $5\log_e$(Probability / 1 - Probability)

= Probability = 1 / 1 + Exp(-score / 5).

(5). To remove the difficulty of dealing with values of infinity, which would occur when an indicants frequency was a zero, we add 0.5 to all numbers when working out the weights of evidence:-

$$W(S/) = \log_e \frac{(AD +0.5) / (ND +0.5)}{A\underline{D} +0.5) / (N\underline{D} +0.5)}$$

where AD = the number of patients with the symptom & disease (CA)

ND = the number of patients who have disease (CA)

$\underline{A}D$ = the number of patients with the symptom but no disease (no CA)

$\underline{N}D$ = the number of patients who have no disease (no CA)

(Cox 1970)

(6). After working out the weights of evidence, 16 GI questions, Age & Sex, & 3 of the tumour markers were decided to be of discriminant value.

(7). These 'scores' were then applied retrospectively to the first patient data set.

(8). By using ROC curves (Metz,1978) a 'cut-off' point for the probability of CA can be reached.

EXAMPLES

To work out a weight of evidence:-

Appetite Change	CA	NO CA
Yes	31	45
No	21	234
	52	279

W(S/D) for 'YES' = $5\log_e$ (31.5/52.5)

(45.5/279.5)

= $5\log_e$ (3.685714286)

= +6.522321714

This is then rounded up to give a 'score' of +7

W(S/D) for 'NO' = $5\log_e$ (21.5/52.5)

(234.5/279.5)

= $5\log_e$ (0.488110468)

= -3.586067649

This is then rounded to give a 'score' of -4

EXAMPLE

After applying the scores to a patient's questionnaire and tumour markers, a series of positive and negative studies will be tabulated as shown here:-

+	-
7	1
2	1
9	3
4	2
4	1
3	2
8	1
8	1
2	1
10	1.5
5	-14.5
+62	

+62 + (-14.5) = +47.5

Then add the Initial score of -27.6 (Prior Probability)

= +19.9 (Final Score)

Then the probability of CA is:- P/1 +exp(-score/5)

= 1/ 1 + exp(-19.9 / 5)

= 1/ 1 + exp(-3.98)

= 1/ (1 + 0.018685639)

= Probability of CA = 0.981657109

(This represents a 98% risk of cancer for this individual)

RESULTS

Questionnaire

The responses to the 18 GI questions for the cancer and benign patients are shown in the table opposite (Table 4.1). As indicated, there are six questions which elicit significantly different responses between those who have gastric cancer and those with a benign upper GI condition. Similarly there are five responses which significantly differ between colorectal cancer and benign large bowel conditions.

The bar chart (Fig 5) indicates that patients with colorectal cancer and gastric cancer are heavily symptomatic having a median number of positive responses of 8 and 7 respectively. In the benign groups there is a considerable spread of positive responses from 0-15 for benign upper GI disease and 0-11 for benign large bowel conditions with median responses of 5 each.

The questionnaire responses to the GI symptoms for the 'normal' group of 'screened' subjects are shown in table 4.2. In these indivduals 73% have 2 or less positive responses to the GI questions in contrast to those individuals with benign conditions of the upper and lower GI tract (13.7% and 28.6%). Few patients with cancers of the stomach and large bowel had less than 2 detectible symptoms on the questionnaire (0% and 5.9%).

The relative sensitivity and specificity of each individual symptom shown to distinguish the cancer subjects from the non-cancer group is further tabulated (Table 4.3). This indicates the relative failure of these symptoms to indicate high

Table 4.1

Percentage frequency of positive responses for question in benign and malignant groups with P value

Q	Ca stomach	Benign stomach	P	Ca Bowel	Benign Bowel	P
Reduced appetite	96.6	53	0.0001*	56.67	29.76	0.0012*
Wt loss no diet	87	54	0.0013*	64.7	30.65	0.0001*
Diff swallowing	33.3	24.6	0.0001*	6.02	5.08	0.8
Food sticks	60	4	0.0031*	6.78	15.85	0.1
Heartburn	48	14.8	0.77	20	25.5	0.49
Nausea	77.4	59.46	0.078	24	42	0.02*
Pain/discomf	56.6	73.13	0.1	249	52	0.7
Bowel action	14.8	5.48	0.12	35	25	0.19
Incomplete emptying	13.3	20	0.42	50	41	0.26
Alt stool frequency	32.4	13.3	0.028*	71.9	37.8	0.0001*
Alt stool appearance	25	12.3	0.13	62.7	36.7	0.0025*
Looseness	33.3	33.3	1	44	56	0.16
Constipation	58.62	18.92	0.0001*	33	31.25	0.79
Blood	10.34	10.67	0.69	46.67	32.94	0.09
Slime	6.9	6.67	0.96	42.37	28.57	0.08

Fisher exact test used in calculating stomach values where no in cell <20

*Significant questions

Table 4.2

Frequency of positive responses per question in the general practice group

	No.	%
Reduced Appetite	55	6.75
Wt loss, no diet	35	4.3
Difficulty swallowing	20	2.45
Food sticking	42	5.24
Heartburn	192	23.76
Nausea	101	12.48
Pain/discomfort	143	17.85
New pain	61	10.34
Bowel habit	32	4.03
Incomplete emptying	66	8.12
Altered stool frequency	50	6.17
Altered stool appearance	59	7.3
Looseness	212	26.1
Constipation	112	13.9
Blood	90	11.3
Slime	57	6.99

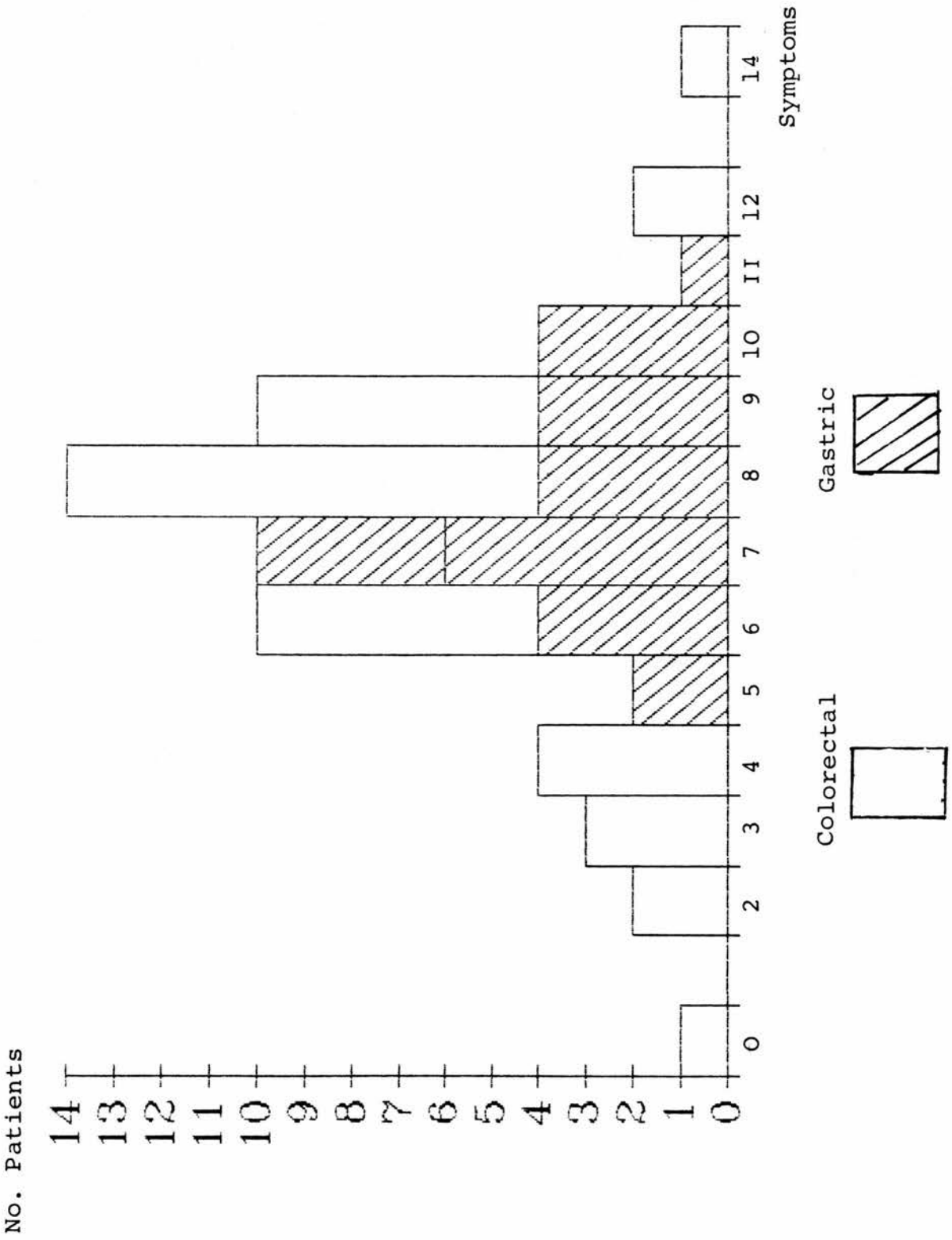
Table 4.3

Sensitivity and Specificity of individual symptoms to indicate risk of cancer- comparing ca v non-c groups

COLORECTAL CANCER	sens %	spec %
Loss appetite	56.67	82
Wt loss	64.7	82.5
Alt stool frequency	71.9	78
Alt stool appearance	62.7	78

GASTRIC CANCER	sens %	spec %
Loss app	96	70
Wt loss	87	71
Diff swallow	33.3	86.5
Food sticking	60	95.5
Alt stool frequency	32.4	90
Constipation	58.6	83.5

Fig 5 Histogram showing frequencies of symptoms in the patients with gastric and colorectal cancer.



risk of cancer on an individual basis. Since a diagnosis is routinely made on the preence of several symptoms the analyses in the subsequent sections should be more pertinent to exploring cancer risk.

Tumour Markers

Single agents

The range of values for the single agents within the groups was large and there was considerable overlap between the groups (Table 4.4). The 95th centile for the benign group values were selected as the cut-off point for cancer and non-cancer values. Thus the cut-off values for CEA, AGP, CRP and GGT were 10 ng/ml, 1.4 g/l, 12 mg/l and 50 U/l respectively (Table 4.5). The mean and standard deviations for the analysis by group are also shown (Table 4.6).

The sensitivity of the markers in detecting gastric cancer, colorectal cancer and all cancers is tabulated (Table 4.7) using this selection criterion. Thus only 27 of 57 colorectal cancers (47.4%) had a CEA level greater than 10 ng/l, and only 14 (48.3) gastric cancers had similarly elevated levels.

The ability to detect early stage cases by this analysis is poor (Table 4.7), with only one third of Dukes' A & B colorectal cancer cases being detected by AGP and CEA, and no early (Stage II) gastric cancers being detected except in 1 case by GGT. However, 67% Dukes' D colorectal cancers were detected by CEA and CRP detected 53.3% of these cases. GGT and AGP were less effective in detecting these cancers with 33% and 46% cases identified respectively. The majority of gastric cases were

Table 4.4
Range of marker values by group

Marker	Benign Range	Cancer Range	GP Range
AGP (g/l)	0.4 - 3.2	0.48 - 3.4	0.4 - 1.94
CRP (mg/l)	1 - 66	1 - 134	1 - 51
CEA (mg/ml)	2.5 - 17	2.5 - 250	2.5 - 17
GGT (U/l)	2 - 450	2 - 400	2 - 470

Table 4.5.

Percentage of patients with a tumour marker value greater than the 95th centile of the benign group

Tumour marker	Cut off value	Cancer %		Normal %
	95th centile	colorectal	gastric	
CEA	>10ng ml^{-1}	47.4	48.3	2.5
AGP	>1.4g l^{-1}	36.8	65	2.6
CRP	>12mg l^{-1}	44	69	2.8
GGT	>50Ul^{-1}	14	10	2.1

Table 4.6
Mean values by group of 4 tumour markers

	Benign		Cancer		GP	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
AGP g/l	0.9759	0.3728	1.4412	0.5990	0.8793	0.2139
CRP mg/l	7.7544	33.9338	21.9691	29.3273	3.4604	5.6290
CEA ml/ml	4.8994	8.2752	40.0234	71.0434	3.7876	2.3578
GGT U/l	30.6023	75.2653	34.5	64.9161	19.1684	34.1498

Table 4.7

Detection of Cancer (%) by Individual Tumour Markers

Tumour Marker	Colorectal		Gastric		All Cancers
	A+B	Total	II	Total	
AGP	31	36.8	0	65	46.5
CRP	37.5	44	0	69	52.3
CEA	31	47.4	0	48.3	47.7
GGT	6.25	14	33	10.4	12.8

advanced (26 of 29) and table (4.7) shows that the acute phase reactant proteins are superior to CEA in the detection of gastric cancer.

In the GP group there were a number of individuals who had levels of a tumour marker above the relevant cut-off point. There were 18 subjects with a CEA > 10ng/ml, but less than 20 ng/ml, 20 subjects with a raised CRP, 19 with elevated AGP. 15 members of the GP group had a GGT greater than 50 U/l with one level at 470 U/l.

The cause of these elevations could be found in some cases for the acute phase reactant proteins AGP and CRP. An elevated marker was found in individuals presenting to their GP with an acute viral illness and a sore throat, colds and flu and also in those with arthritis. Smoking accounted for the majority of elevated CEA's with the mean for smokers being 3 ng/ml higher than for non-smokers in the study.

Combination of Analytes

Table (4.8) shows the impact of defining a patient as having cancer if one of the agents in the combination is positive. Thus using the combination of CEA + CRP, 5 additional colorectal tumours were detected but 57 subjects in the non-cancer group were also positive (6%). In this way one additional gastric cancer would also be detected. By adding further analytes into the combination whilst 2 additional colorectal and 1 gastric cancer were detected the specificity as expected started to fall. Thus the 4 marker combination identified 66 (65%) of the cancers at the cost of a 10.5% false positive rate.

Table 4.8

Combination of Analytes to detect cancer

Tumour Marker	Colorectal		Gastric		Total	Specificity
	n	%	n	%	%	%
CEA	27	47.4	14	48.3	47.7	95
CEA + CRP	32	56	21	72.6	61.6	94
CEA + ARP + AGP	33	57.9	21	72.6	62.8	93
CEA + AGP + CRP + GGT	34	59.6	22	75.8	65.1	89.7

Multivariate Analysis

The initial data set was used to fit a logistic model to discriminate the cancer from the non-cancer group. Using only the biochemical data, 36 (67%) of the 54 cancer patients were correctly classified, with a false positive rate of only 5%. The 18 cancers missed by this simple discriminant included 5 patients with liver metastases from colorectal cancer and 2 patients with advanced gastric cancer. A similar analysis using only the 18 GI oriented questions on the questionnaire correctly classified 60% cancers with a 5% false positive rate. In a logistic analysis using both the questionnaire and biochemical data, 50 cancers (92%) were separated from the non-cancer groups, with a similar 5% false positive rate (Table 4.9). This is a significant improvement on both the questionnaire and biochemical data when used individually ($p<0.02$ X^2 test). The cancers misidentified were 2 colorectal cancers (Dukes' stage C + D) and 2 gastric cancers (stage II + IV).

The fitted model is determined by the discriminant function (log to base 10):

$$y = 0.605\ (\text{sex}) + 0.112\ (\text{age}) \_ 2.73 \log (\text{CRP}) + 5.33 \log (\text{CEA}) - 4.09 \log (\text{GGT}) + 1.05\ (\text{wt. loss}) + 0.968\ (\text{bowel habit}) + \text{constant}\ (8.4)$$

and the probability of cancer is then $P = \exp(y)/(1 + \exp(y))$.

The "optimal" cut off point for these values to indicate cancer is $p \geq 0.275$ (Fig 6).

By applying this criterion to the second data set, 28 of

Fig 6 Histogram of predicted probability of cancer using multivariate analysis (initial data set).

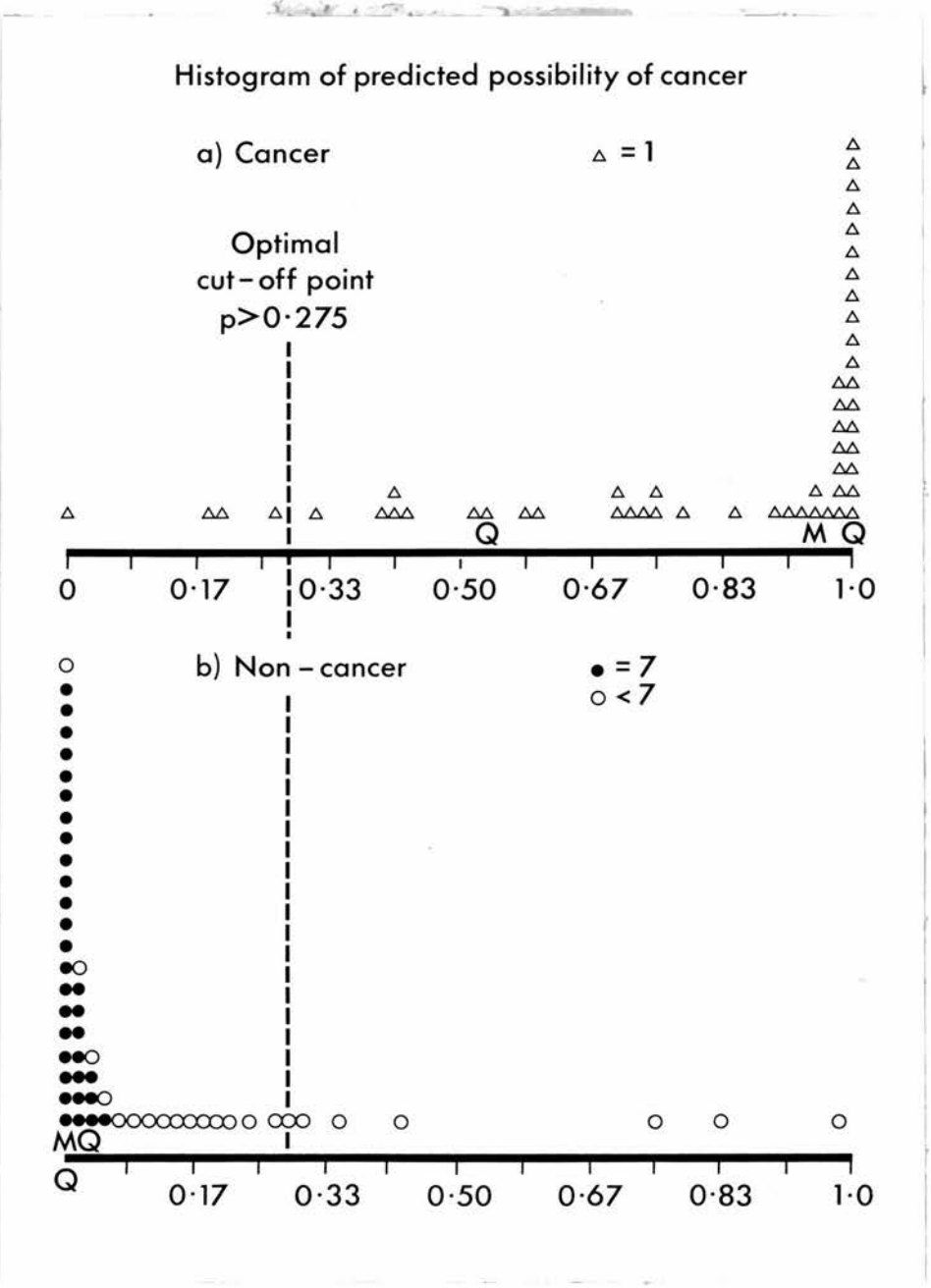


Table 4.9
Results of Stepwise Logistic Regression - analysis applied to the initial data set

Biochemical markers

	Predicted				
	Cancer	Non-cancer			
Actual Ca	36	18	54	Sensitivity	66.7
Actual Non-ca	15	265	280	Specificity	94.7
	51	283	334	Pos Predictive Value	71.6
				Neg Predictive Value	93.6
				Overall accuracy	90.1

Questionnaire

	Predicted				
	Ca	Non-Ca			
Actual Ca	33	21	54	Sensitivity	61
Actual Non-Ca	14	266	280	Specificity	95
	47	287	334	Pos Predictive Value	70.2
				Neg Predictive Value	92.7
				Overall accuracy	89.5

Biochemical Markers + Questionnaire

	Predicted				
	Ca	Non-Ca			
Actual Ca	50	4	54	Sensitivity	92.59
Actual Non-Ca	14	266	280	Specificity	95
	64	270	334	Pos Predictive Value	78.1
				Neg Predictive Value	98.5
				Overall accuracy	94.6

Chi square = 7.82 ; $p < 0.02$

32 cancers (88%) were selected but the specificity fell to 89% (Table 4.12). The 4 cancers misclassified as low risk for cancer were all colorectal (Dukes' C).

The application of this type of analysis to the patients with benign disease, lead to 26 of the 168 individuals being identified as at "high risk" of cancer. However, included in the 26 there were 4 subjects with gastric ulceration or polyps and 4 patients with large colonic tubular polyps and villous adenomas. Thus the system detected further "high-risk" potentially premalignant conditions which clinicians would wish to investigate.

Fifty-six subjects of the 720 individuals in the GP study were classified by the analyses to be at high risk for cancer. Only seven were investigated but no neoplasia was detected (4 diverticular, 1 haemorrhoids, 1 colonic inertia, 1 duodenal ulcer). In the remainder, raised acute phase reactant proteins (APRP's) due to upper respiratory tract infections (the reason for the GP consultation) may have caused the falsely high probability value. To date with a follow up of 18 months no cancers have been identified in these 56 subjects. However, within the control GP population one woman has presented with obstructive jaundice secondary to carcinoma of the pancreas. She was entirely asymptomatic at the time of initial screening.

Likelihood Ratio Analysis

Using the same initial test data set as for the multivariate analysis the weights of evidence were calculated for the GI questions and tumour markers. GGT was found to be of no

Table 4.10
Scoring System - Cancer group v benign and GP groups

1.	Appetite Change		12.	Change in Appearance	
	Yes	+7		Yes	+8
	No	-4		No	-4
2.	Appetite Decreased		13.	Diarrhoea	
	Yes	+2		Yes	+1
	No	-14		No	-1
3.	Weight Decreased		14.	Constipation	
	Yes	+9		Yes	+5
	No	-6		No	-2
4.	Diff Swallow		15.	Blood	
	Yes	+4		Yes	+3
	No	-0.5		No	-1
5.	Food 'Sticking'		16.	Slime	
	Yes	+5		Yes	+5
	No	-1		No	-1
6.	Nausea & Vomiting		17.	AGP	
	Yes	+3		< 1.19	-5
	No	-1		> 1.2	+10
7.	Pain		18.	CRP	
	Yes	+4		0-1	-9
	No	-2		2-7	-1.5
				8+	+9
8.	Different Pain		19.	CEA	
	Yes	+3		< 4.9	-7
	No	-8		5-6.9	0
				7-9.9	+5
9.	Frequency			10-19	+8
	0	-3		20+	+25
	1	+4			
10.	Tenesmus				
	Yes	+4		Male	+2
	No	-2		Female	-2
11.	Change in Frequency				
	Yes	+8			
	No	-4		Age <50	-13
				50-59	-5
				60-69	+1
				80+	+15

Initial Starting Score -27.6

practical value for discriminating between the groups and has been eliminated from further calculations. The final weights or scores are shown opposite (Table 4.10) where the prior probability value is noted to be -27.6.

The individual scores for each subject can then be plotted (Fig 7) and by applying receiver operator characteristics (ROC) curves the optimum "cut-off" point can be estimated. In this case a value of -15 as a score or a probability of greater than 0.05 has been taken as our cut-off value (Figs 7 and 8). Using these values, the results for the questionnaire, tumour marker data and the combination of both are shown for the initial data set (Table 4.11).

Once again the combination of data from the questionnaire and tumour markers is superior. The eight cancers missed by the combination of the questionnaire and tumour marker data were one stage IV gastric cancer, 3 rectal cancers (Dukes' B(2) and C) and 4 colonic cancers (2 Dukes' B and 2 Dukes' D). Three of the four GP subjects with an 'at risk' score were symptomatic at the time of completion of the questionnaire. On review one was still symptomatic as well as FOB positive and was fully investigated with only diverticular disease of the sigmoid colon being found. In the fourth, a smoker with an elevated CEA, presented with bronchitis which would account for the elevation of ARP & CRP which made him positive for the study. The false positives from the benign group included diagnoses of peptic ulcer and gastritis in 4 subjects, perianal conditions, 1 villous adenoma of rectum, diverticular disease and the irritable bowel syndrome.

Fig 7 Distribution of scores for three groups using Log Likelihood ratio (initial data set).

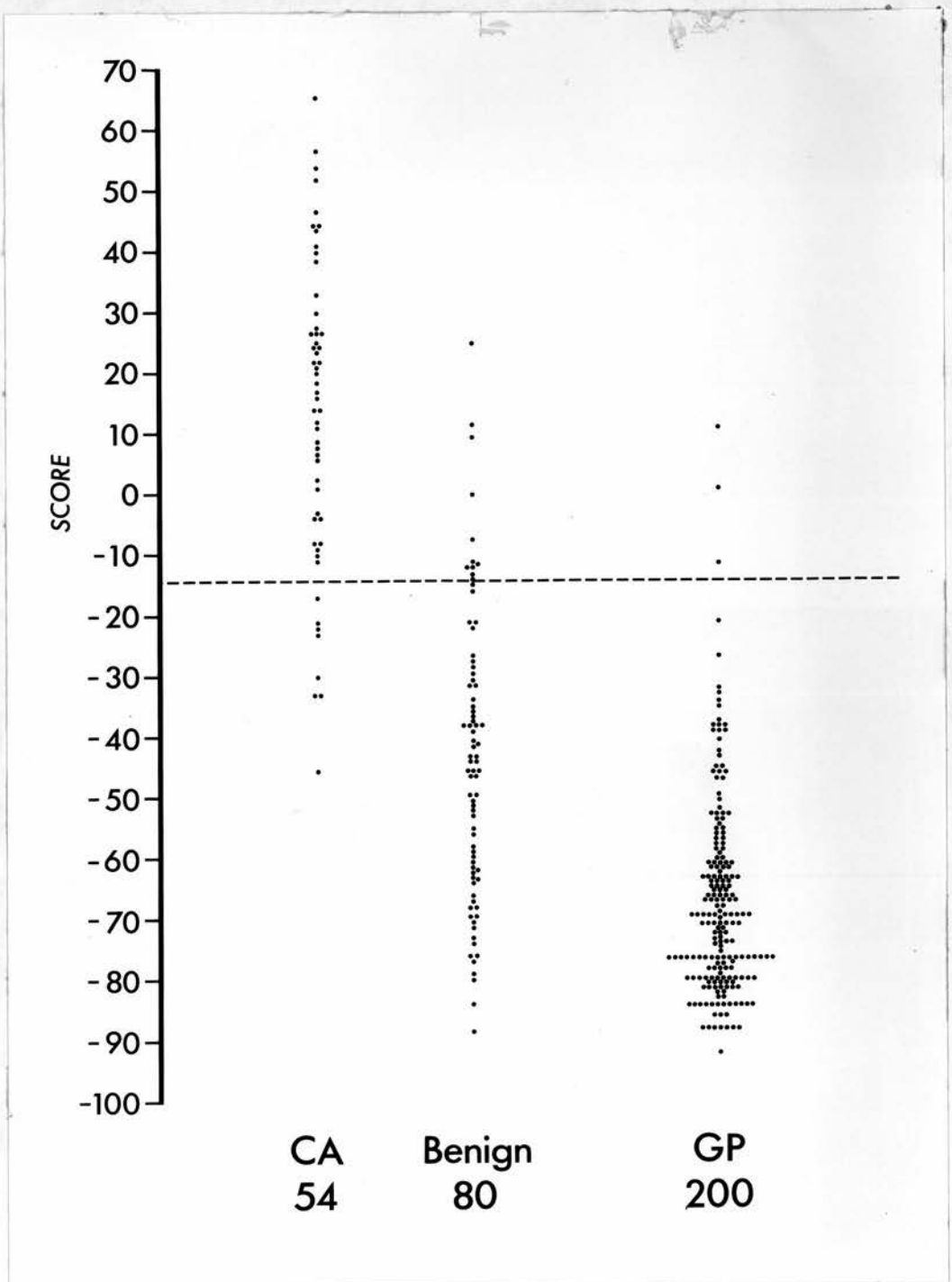


Fig 8 Probability distributions for cancer in the three groups using the Log Likelihood Ratio (initial data set).

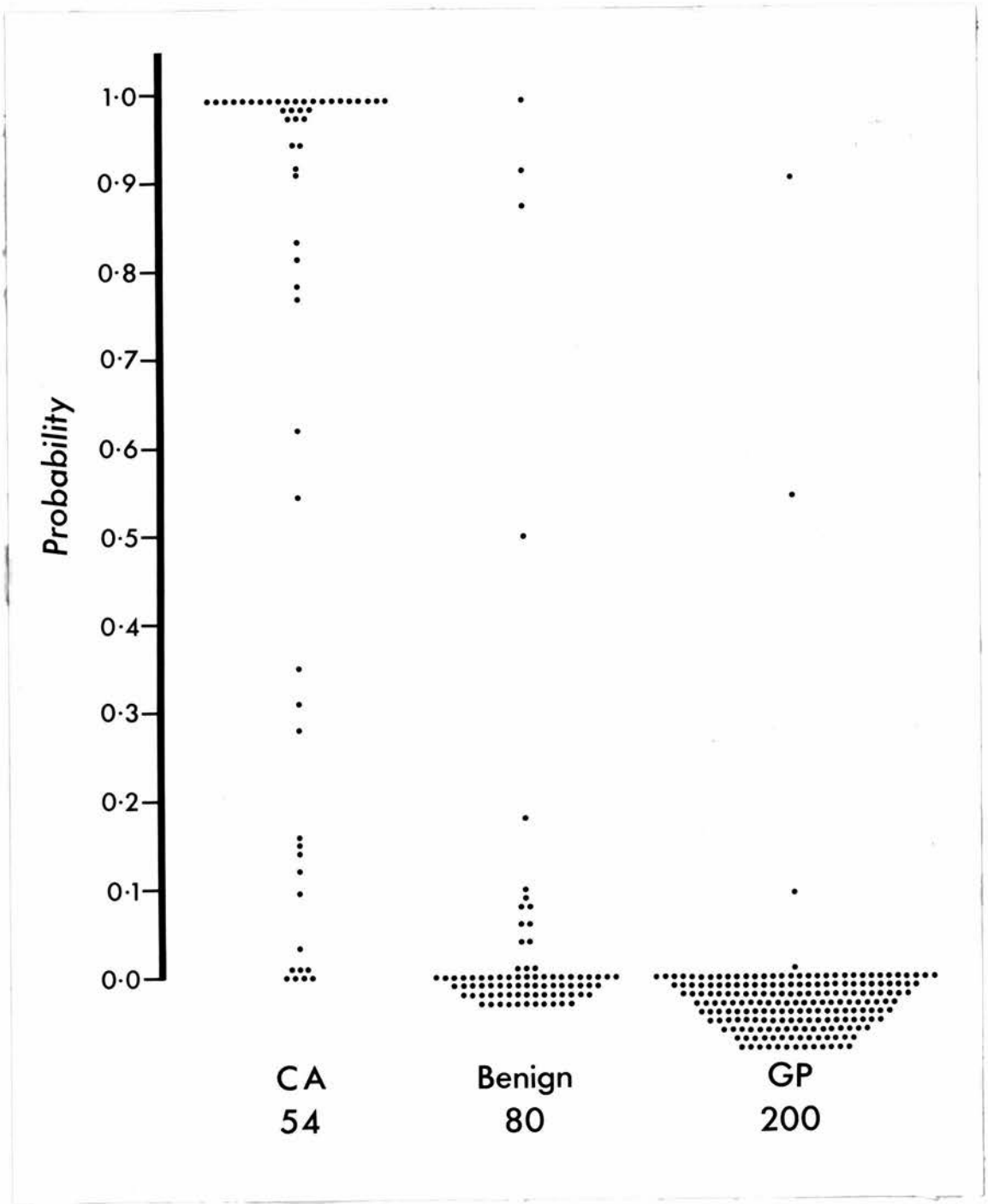


Table 4.11

Results of Log-Likelihood Ratio Analysis applied to the initial data set

Biochemical Markers

		Predicted			
		Cancer	Non-cancer		Sensitivity 59.3
					Specificity 92.9
Actual	Ca	32	22	54	Pos Predictive Value 61.5
	Non-ca	20	260	280	Neg Predictive Value 92.2
		52	282	334	Overall accuracy 87.4

Questionnaire

		Predicted			
		Cancer	Non-cancer		Sensitivity 70.4
					Specificity 94.3
Actual	Ca	38	16	54	Pos Predictive Value 70.4
	Non-ca	16	264	280	Neg Predictive Value 94.3
		54	280	334	Overall accuracy 90.4

Biochemical markers plus Questionnaire

		Predicted			
		Cancer	Non-cancer		Sensitivity 85.1
					Specificity 94.6
Actual	Ca	46	8	54	Pos Predictive Value 75.4
	Non-ca	15	265	280	Neg Predictive Value 97
		51	273	334	Overall accuracy 93.1

Table 4.12

Comparison of Results between log likelihood ratio method and multivariate analysis for Second data set

Log likelihood ratio

		Predicted			
		Cancer	Non-cancer		Sensitivity 84.37
					Specificity 98
Actual	Ca	27	5	32	Pos Predictive Value 69.2
	Non-ca	12	596	608	Neg Predictive Value 99.16
		39	601	640	Overall accuracy 97.34

Multivariate analysis

		Predicted			
		Cancer	Non-cancer		Sensitivity 87.5
					Specificity 88.8
Actual	Ca	28	4	32	Pos Predictive Value 29.2
	Non-ca	68	548	608	Neg Predictive Value 99.2
		96	552	640	Overall accuracy 88.75

To parallel the multivariate approach the second data set was processed using the cut-off derived from the initial data set. In contrast to the multivariate method the specificity did not fall but improved to 98.5% (Table 4.12). A comparison of results is shown in this table for the two approaches. The distribution of scores and probability of cancer for the second data set using the log likelihood method are shown (Figs 9 and 10).

The cancers missed by the log likelihood ratios in the second data set were 2 gastric cancers (Stage II + IV) and 2 rectal cancers (Dukes' C + D) and one splenic flexure cancer (Dukes' Stage C). 7 benign cases were declared as cancer. These included 2 gastric polyps and one gastric ulcer, a colonic polyp, 2 cases of diverticular disease and one individual with the irritable bowel syndrome. Two GP subjects were also felt to have cancer. In one the positive responses to the GI question could be attributed to her chronic renal failure and in the other a raised CRP and AGP were contributory to his predicted high risk of cancer.

Table 4.12. illustrates the high positive predictive yield for the log likelihood ratio method (69%) which is considerably higher than for the multivariate approach (29%).

Further Application of Log Likelihood Ratios to the earlier diagnosis of gastric cancer.

In view of the attempts of Mann and his colleagues (1983) to establish 'risk' for significant upper gastrointestinal disease using discriminant analysis techniques, a further investigation of log likelihood ratios to specify risk of gastric cancer has been

Fig 9 Distribution of scores for three groups using Log Likelihood Ratio (second data set).

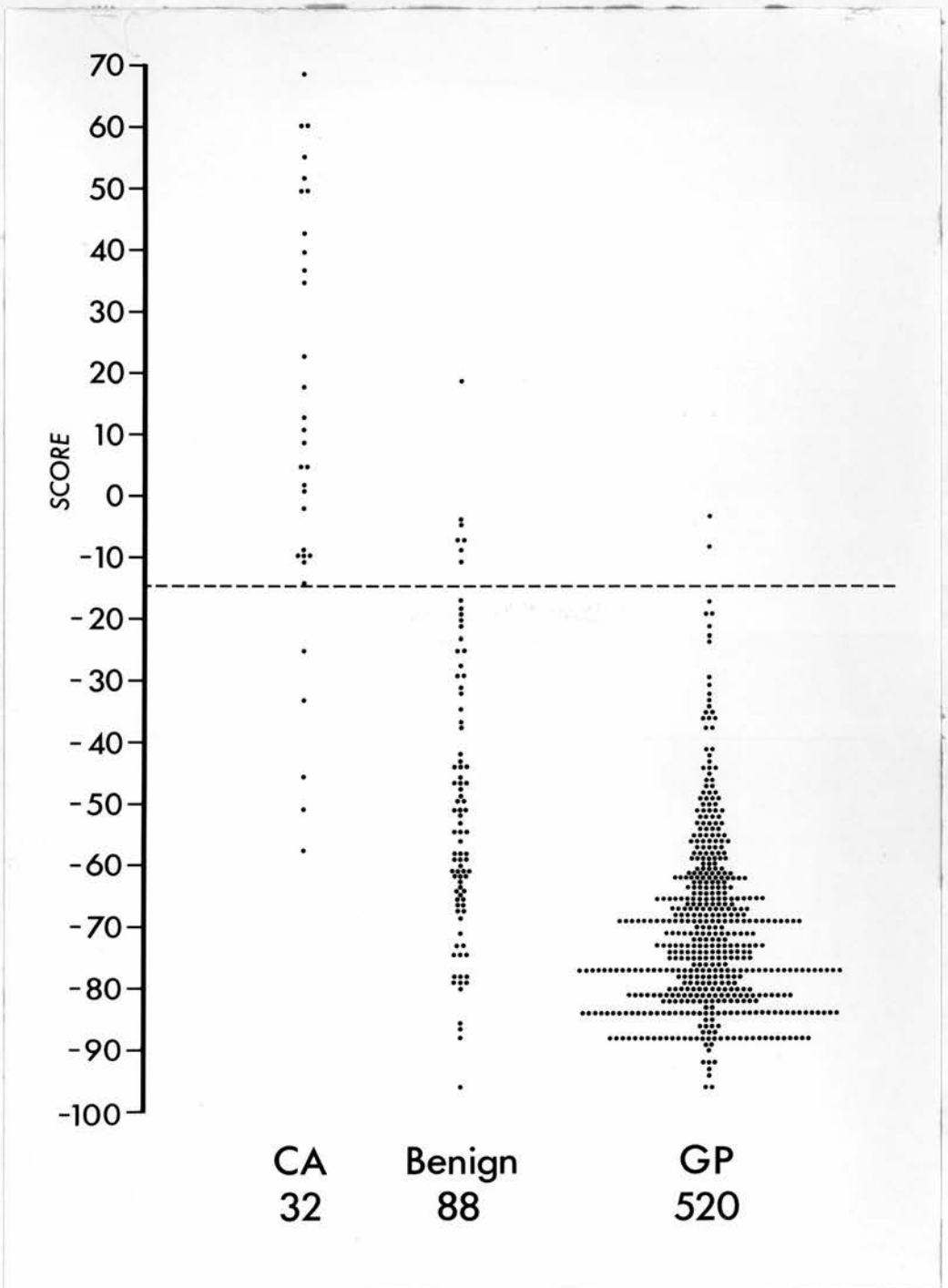


Fig 10 Probability of cancer in three study groups using Log Likelihood Ratio (second data set).

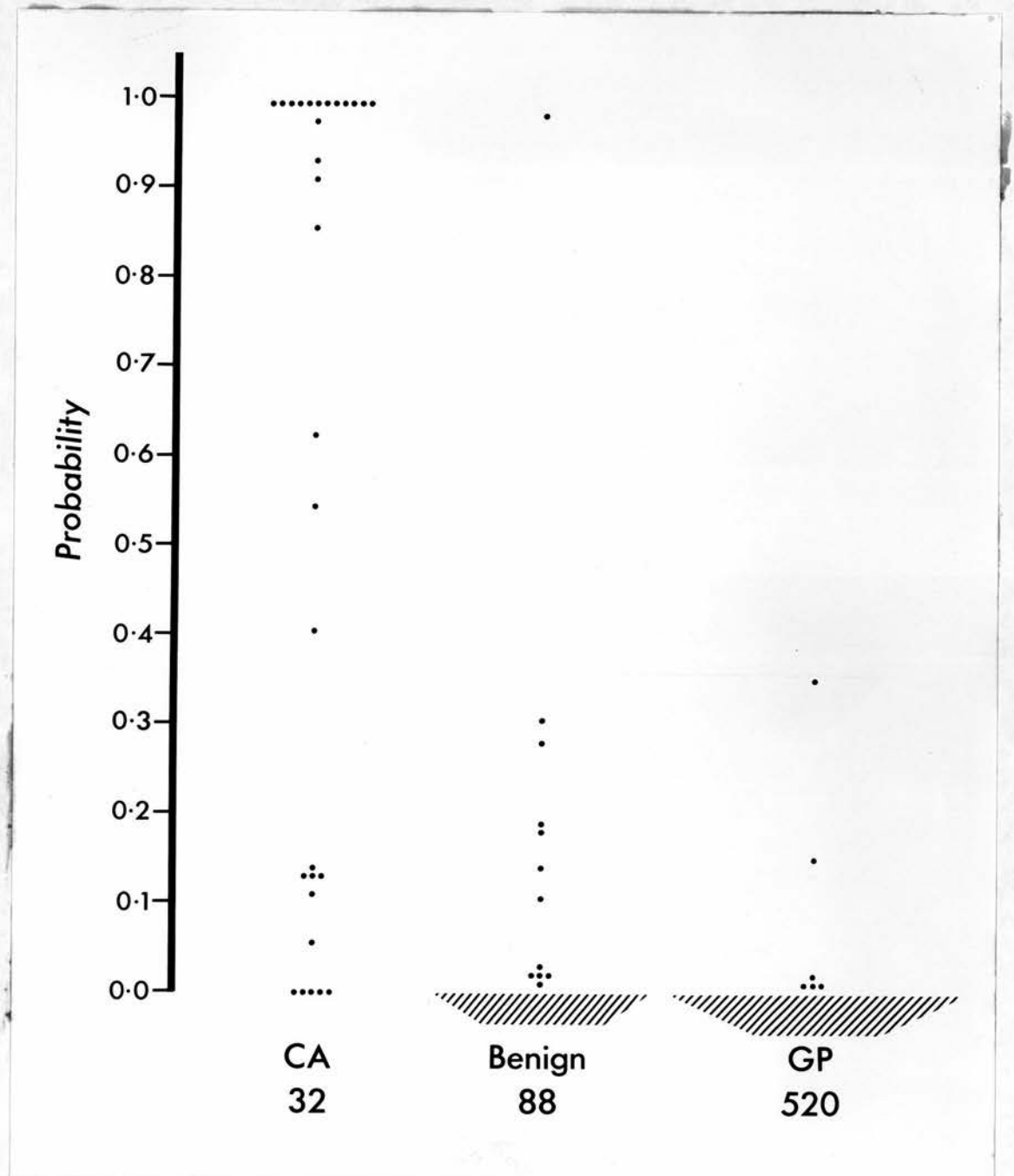


Table 4.13
Gastric Cancer v Rest (Upper GI Genign + GP)

Appetite Change	Yes	+8
	No	-10
Appetite Decreased	Yes	+1
	No	-10
Weight Decreased	Yes	+11
	No	-11
Diff Swallowing	Yes	+8
	No	-2
"Sticking"	Yes	+8.5
	No	-4
Heartburn	Yes	+3
	No	-2
Nausea & or Vomiting	Yes	+6
	No	-6
Pain	Yes	+4
	No	-2
Different Pain	Yes	+2
	No	-4

Age	
<59	-5
60-69	+1
70-79	+8
80+	+14

Male +1
Female -1

Starting Score -27.6

performed.

As in the previous analyses an initial data set and a second data set have been assessed. The initial data set comprised the 29 gastric cancers, 64 benign gastric duodenal and oesophageal lesions and 200 GP cases from the main study. The symptoms of a further 71 gastric cancers (20 early i.e. Stage I) and 100 patients with endoscopically proven benign disorders of the stomach (38), oesophagus (18) and duodenum (44) were recorded in a retrospective review of their case records. This data was then used as the second data set to give an indication of the positive predictive value of the scoring system thus derived from the initial data set (Table 4.13).

A prospective study was then established to compare a consultant clinician's assessment of risk of gastric cancer in any new referral to a dyspepsia clinic with the predicted risk defined by this newly generated scoring system. The clinician was then also asked to state the likelihood of peptic ulceration to be present in each subject. He did this blind with the data being collated separately for estimation of the scoring index. Three hundred individuals were assessed in this way and the final clinical diagnoses are shown (Table 4.16).

The values obtained from the initial data set for the responses to the upper GI questions are shown opposite (Table 4.13). Once again the starting score was taken to be -27.6.

Applying these values the sensitivity for cancer with the system was 79.3% for the initial data set with a specificity of 94.7% (Table 4.14). When the scoring system was applied to the

second data set the sensitivity became 81.7% with a specificity of 94% (Table 4.14). Thirteen (65%) of 20 early gastric cancers were detected and 45 (88%) of 51 advanced gastric cancers were also identified as being high risk individuals (Figs 11 + 12). The patients felt to be at risk from the benign group included 6 individuals with gastric ulcers, 2 subjects with peptic stricture and 3 individuals with chronic duodenal ulceration. No subject in the GP control group fell into the at risk group.

Table (4.15) shows an alternative way of handling the probability data in which risk of gastric cancer in the second data set is defined as $P>0.05$, risk of sigificant benign disease as $0.000018 < P < 0.05$, and any individual with a risk lower than 0.000018 as being 'normal'.

The comparison of the predicted risk for gastric cancer in a dyspeptic individual for the scoring system and the clinician is shown in Table (4.17). The table shows a remarkable similarity in the overall performance for the scoring system compared to the clinician. Whilst the clinician's specificity was excellent at 95%, he only spotted as high risk four of seven early gastric cancers compared to all seven being selected as high risk by the scoring system. By adopting the high, intermediate and low risk categories all the cancers were detected by the scoring system and only one was missed by the clinician (Table 4.18). At the same time there was considerable accord as to which patients were felt to harbour no significant disease and 20% fell into this category for each method of assessment.

Table 4.14

Log likelihood ratio analysis to predict risk of gastric cancer

Initial data set

		Predicted			
		Cancer	Non-cancer		Sensitivity 79.3
					Specificity 94.7
Actual	Ca	23	6	29	Pos Predictive Value 62.2
	Non-ca	14	250	264	Neg Predictive Value 97.7
		37	256	293	Overall accuracy 93.2

Second data set

		Predicted			
		Cancer	Non-cancer		Sensitivity 81.7
					Specificity 94
Actual	Ca	58	13	71	Pos Predictive Value 82.9
	Non-ca	12	188	200	Neg Predictive Value 93.5
		70	201	271	Overall accuracy 91

Fig 11 Distribution of scores for dyspepsia study (second data set).

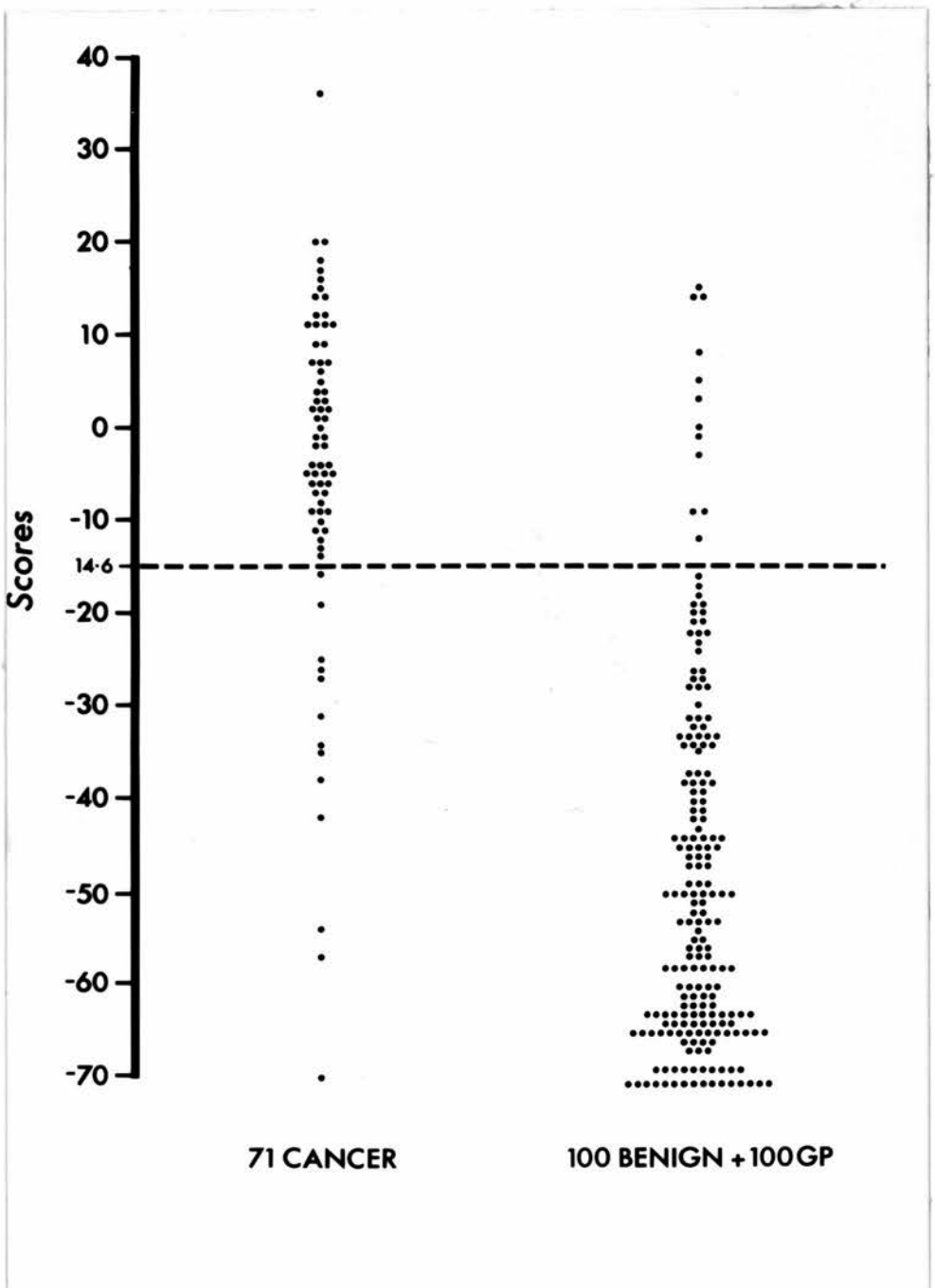


Fig 12 Probability of gastric cancer in dyspepsia study (second data set).

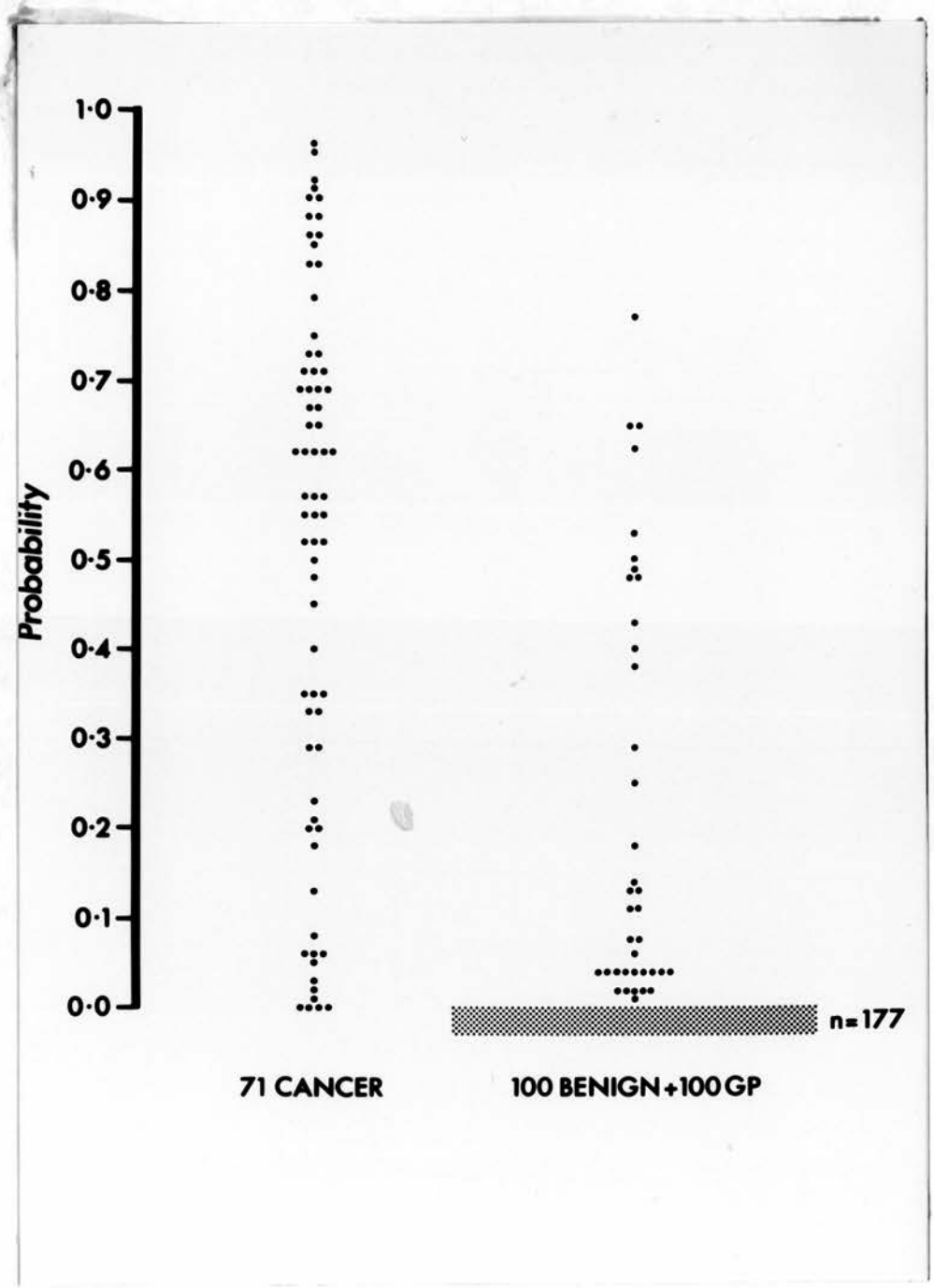


Table 4.15

Distribution of subjects according to "risk" category for second data set

	Cancer	Benign disease	'Normal'	
High Risk	58	12	0	70
Intermediate	11	74	18	103
Low Risk	2	14	82	98
	71	100	100	271

High risk	Probability > 0.05	score > -14.5
Low risk	P< 0.000018	score < -27

Table 4.16

Final Diagnosis in 300 Prospective Subjects

Gastric Cancer	16	(4 EGC)
Other cancers	5	(pancreatic oesophageal)
Benign	57	Oesophagitis
	3	Oesophageal strictures
	25	Gastric Ulcers
	50	Duodenal Ulcers
	4	Gall stones
'Functional'	140	Endoscopy and ultrasound negative

Table 4.17

Comparison of clinicians prediction of cancer risk with log likelihood ratio risk for 300 prospective subjects with dyspepsia

Log likelihood Ratio

	Predicted				
	Cancer	Non-cancer		Sensitivity	93.7
				Specificity	89.4
Ca	15	1	16	Pos Predictive Value	33.3
Actual Non-ca	30	254	284	Neg Predictive Value	99.6
	45	255	300	Overall accuracy	89.6

Clinician

	Predicted				
	Cancer	Non-cancer		Sensitivity	56.2
				Specificity	94.7
Ca	9	7	16	Pos Predictive Value	37.5
Actual Non-ca	15	269	284	Neg Predictive Value	97.4
	24	276	300	Overall accuracy	92.6

Table 4.18

Distribution according to 'risk' for Prospective Group:
Comparison of clinician's assessment with log likelihood ratio

Log Likelihood Ratio

	Cancer	Benign	'Normal		
High	18	19	6	Sensitivity	85.7
Intermediate	3	103	89	Specificity	91
Low	0	17	45	Pos Predictive value	41.86
				Neg Predictive value	98.8
				Overall	90.7

Clinicians Assessment

	Cancer	Benign	'Normal'		
High	12	6	4	Sensitivity	57.1
Intermediate	8	112	96	Specificity	96.4
Low	1	21	40	Pos Predictive value	54.5
				Neg Predictive value	96.8
				Overall	93.7

high risk $p > 0.05$
low risk $p < 0.000018$

Discussion

Many authors have shown that a proportion of colorectal and gastric cancers may be relatively slow to both grow and metastasise and that the longer symptoms are present prior to diagnosis the better is the prognosis (Irvin and Greaney, 1977; McDermott et al, 1981). It may therefore seem illogical to divert resources to the earlier temporal detection of symptomatic cancers if the survival for most active tumours will not be affected (Austin, 1980). Welch and Donaldson (1974) have indeed shown that whilst the delay to diagnosis of rectal carcinoma was reduced from 7 months to 2 months no real survival benefit accrued to these patients. However, Holliday and Hardcastle (1981) have shown that many individuals presenting with large bowel obstruction, secondary to colorectal carcinoma, had presented to their GP's within the previous 12 months with highly suggestive symptomatology of cancer. In these patients the mortality for surgical treatment was 38% compared to 7% for elective resection for cancer. Similarly Waldron et al (1986) noted that 51% of their colorectal cancer patients presented at an age of 70 years or more and of these 58% presented as emergencies with a subsequent 38% operative mortality. Both groups of workers feel that earlier diagnosis would reduce the operative mortality for colorectal cancer,possibly overall mortality, and advocate stronger efforts to detect these cancers at a period before obstruction is present. For gastric cancer there is some evidence that earlier temporal detection in the symptomatic group will increase the resection rate and confer improved palliation for

these patients (Fielding et al, 1985).

It was the apparent success of Mann et al (1983) and De Mello et al (1983) using sophisticated statistical methods to define risk for significant benign gastrointestinal pathology or cancer that stimulated this further appraisal of questionnaire and tumour markers to define risk of colorectal or gastric cancer in a symptomatic individual. This in turn could be used to determine priority for investigation in symptomatic individuals. Consequently a reduction in the delay to diagnosis of these cancers either at the GP or hospital level could be achieved (MacAdam 1979; Holliday and Hardcastle 1981; MacArthur and Smith 1984).

The problems of using a single tumour marker for preoperative cancer detection are again well demonstrated in this study. Even by taking the 95th centile value of the patients with benign disease as the cut-off point for CEA detecting cancer, there are still 2.5% of the normal population with elevated CEA levels (nearly all smokers), whilst the sensitivity for cancer overall was only 47%. Whilst the level of cut-off at 10 ng/ml is twice that of the manufacturer's recommendation, the sensitivity for CEA in detecting Dukes' A + B cancers at 31% and 67% for Dukes' D cancers is consistent with many reported series (Dhar et al, 1972; Lo Gerfo et al, 1972; Lawrence et al, 1972; Shuster et al, 1974; Livingstone et al, 1974; Miller et al, 1974; Booth et al, 1974; Luporini et al, 1976; Beatty et al, 1979). Similarly for gastric cancer CEA detected less than 50% of advanced lesions and this is similar to other reported series (Tatsuta et al 1980;

Satake et al 1981; Staab et al 1982). Even the simple additive effect of combinations of markers as reported by Chu et al (1982) has done little to increase the sensitivity for cancer while increasing the false positive rate.

Similarly the simple analysis of symptoms (Tables 4.1,4.2,4.3) emphasises how difficult it is to interpret a single symptom to make a diagnosis of cancer. For example, rectal bleeding in a patient older than 50 years might normally be considered worthy of investigation by digital rectal examination, proctosigmoidoscopy and barium enema. Certainly 47% of colorectal cancer subjects in this study complained of this symptom but so did 33% of benign control subjects and 11% of GP subjects making this symptom statistically insignificant as a risk factor for colorectal cancer. However, in clinical practice diagnosis is seldom dependent upon a single symptom or sign but usually as the combination of several symptoms. But even using the multivariate approach as proposed by Mann et al (1983) the ability to discriminate between cancer and non-cancer was not great (60%) and serves to emphasise the considerable overlap of symptoms between normal subjects, symptomatic subjects with benign conditions and those with colorectal and gastric cancer. Whilst the conditions are different from those proposed by Mann et al (1983) these findings do raise doubts concerning the validity of symptom complex analysis alone to determine cancer risk.

It was the combination of the questionnaire and tumour marker data however that lead to a significant increase in prediction of cancer by the statistical methods ($p < 0.02$, for

stepwise logistic regression, Table 4.9). Using the optimising function on the BMDP package the probability cut-off was determined. Similarly for the log likelihood ratio (LLR) method the combination of symptoms and tumour markers was more accurate overall and receiver operator characteristic curves were used to give confidence to the cut-off scores and probability levels (Metz, 1978). Using these cut-off values and the discriminant functions derived in the initial data set encouragingly high sensitivities were maintained for the prediction of cancer in the 2nd data set, and were equivalent to 88% and 84.4% respectively for the SLR and LLR methods (Table 4.12). However, whilst the specificity for the log likelihood ratio method was maintained that of the stepwise logistic regression fell to 89%. This difference is further reflected in the positive predictive values for the second data set. Since the positive predictive value more accurately assesses the validity of an agent then the log likelihood method appears superior at 75% compared to 29% for the stepwise logistic regression analysis. It is not immediately clear why such a difference should exist between these two methods. One possible explanation is that whilst the logistic regression method relinquishes any value that does not improve the discrimination of the cancer group from the non-cancer group to the 5% level the LLR retains all values where there is any difference between the groups. By retaining these values, their cumulative weight may influence the outcome.

As demonstrated in Chapter 2, the general population are frequently symptomatic with 27% having 3 positive responses to

the GI symptoms on the questionnaire. It was therefore felt important that any method to detect risk of cancer from within a symptomatic population should take acount of this prevalence of symptomatology. This has not been deemed necessary by Mann et al (1983) or Davenport et al (1985) who used subjects being endoscoped as their controls. This might make the general application of their systems at the primary referral level i.e. the initial GP consultation, which was their first intention, somewhat suspect. It is therefore gratifying to see only 56 (7.7%) of the GP subjects were felt to be at high risk for cancer using the stepwise logistic regression analysis. Of the seven investigated on clinical grounds no neoplastic disease was found and neither was there any tumour detected in the remaining 49 over 18 months follow-up. One patient has presented with obstructive jaundice secondary to a pancreatic neoplasm 12 months after her initial screening visit. She was entirely free of symptoms at the time of screening and all her markers were within normal limits. Twenty-six of the benign disease group (15%) would have been classified as being at high risk of cancer. Within this group, patients with potentially premalignant conditions e.g. gastric polyps, gastric ulcers and colorectal polyps were commonly declared as being at high risk for GI cancer (8 of 26) and this may represent success rather than failure of a system to determine priority for investigation in these individuals and would fit Mann's category of significant disease (Mann et al, 1983).

The follow-up of these 26 "high risk" individuals from within the benign control group has revealed one cancer already.

This man with upper GI symptoms who had a negative barium meal and endoscopic examination, re-presented 6 months later and was found to have a carcinoma of the fundus of the stomach. The probability of cancer at the first presentation was 80% using the questionnaire and tumour marker data.

Such results in a preliminary study must always be met with caution. Whilst the number of non-cancer subjects used in this study is larger than previous reports, the overall study is small and prolonged periods of prospective data collection would be necessary to fully evaluate the potential of this approach. Furthermore, to miss between 8 and 13 cancers (SLR and LLR respectively), the majority of which were potentially curable is not to be considered lightly. However, all three symptomatic Dukes' A cancers and 13 of 14 Dukes' B cancers were detected by the stepwise logistic regression method but 4 Dukes' B cases were missed by the log likelihood approach. Both systems failed to identify the two cancers detected as part of a work-up of iron deficiency anaemia. However, a symptom questionnaire cannot detect asymptomatic cancers, and it is stressed that the object of this exercise was to identify risk for cancer and therefore to define priority for investigation when dealing with a symptomatic population. Any patient with persistent symptoms could easily be referred sooner, irrespective of the probability value. An alternative to this would be to define high risk, intermediate risk and low risk groups for cancer. All high risk individuals would be investigated urgently, intermediate risk reviewed and investigated for persisting symptoms and the low group reviewed by

the GP or at the patient's request. This has been performed in the first study of tumour markers and symptoms using high powered statistical analyses and these results are available in the Appendix (Marshall and Chisholm, 1985).

The basic cost for this approach must be considered as a balance between expenditure on the biochemical tests versus any reduction in investigation costs by reduced referral rates. The biochemical analyses cost £5.00 per head (including labour, but excluding overheads) the brunt of which is the price of the CEA tests. This could be offset by the reduction in unnecessary investigations where the probability of cancer is extremely low.

As stated earlier the aim of this study was to investigate a simple means of predicting the risk of cancer of colon and stomach which would be readily acceptable to the public and not time consuming for the clinician. However, there is no reason why the data could not be applied simply to one or other cancer to study risk specifically for either one.

When applied to colorectal cancer, the SLR system identified 44 (80%) of the cancers as being high risk and only 4% of benign colorectal lesions as high risk. Whether this approach would have much value is open to question, since both Leicester and his colleagues (1983) and Farrands et al (1985) have shown that FOB testing in patients with lower gastrointestinal symptoms are extremely reliable. Leicester et al (1983) found 85% colonic cancers and 50% rectal cancers were FOB positive and Farrands et al (1985) had a 100% sensitivity for colonic cancer in their consecutive outpatient series. In both these series a modest

false positive rate was encountered and clearly a priority group for full colonic assessment was defined. Clamp and Wenham (1984) however, have shown that the combination of computer predicted risk using a structured questionnaire plus FOB testing in a general practice setting is more effective than either agent used individually. It is regretted that in this current study the cancer and benign disease groups did not undergo FOB testing to permit further comparison.

The potential for symptom analyses however may well be best realised in the management of upper GI symptoms. Both Mann et al (1983) and Davenport et al (1985) have successfully used scoring systems to determine risk of harbouring peptic stricture, peptic ulcer and to a lesser extent gastric cancer. Davenport et al (1985) however tested their own patients responses using Mann's scoring index (Mann et al, 1983) and found that a high percentage of their patients with serious pathology were classed as low to intermediate risk. They further found that one third of gastric cancers were missed with Mann et al's system. With the great interest that now exists in the increased detection of early gastric cancer (Fielding et al, 1980; Ward et al, 1985, 1986; Allum et al, 1986) calls for increased upper GI endoscopy to exclude the presence of early gastric cancer in new onset middle-age dyspeptic patients (Ward et al, 1985; Allum et al, 1986) are becoming commonplace. However, Holdstock et al (1979) and Mann et al (1983) claim that it will be impossible to service open-access endoscopy requirements to meet these demands. It therefore seemed appropriate to assess whether within the broad group of patients

with "dyspepsia" there were certain combinations of symptoms which could readily identify cancer from non-ulcer dyspepsia, gastritis, peptic ulcer and motility disorders.

It was surprising considering the overlap of symptoms within these diagnoses that the log likelihood system was able to identify over 65% of the EGC and 88% advanced gastric cancers in the retrospective study. The fact that many of these false negative cases had no symptoms and were found only as part of the investigation of anaemia is not particularly a failure of the system which relies on symptoms being present, but merely a reflection of the spectrum of presentations of gastric cancer. Furthermore, the false positive cases detected included 6 gastric ulcers, 2 peptic strictures and a pyloric stenosis which all require rather different management to the routine duodenal ulcers and non-ulcer dyspepsia.

Once again this is only a preliminary investigation and little weight can be attached to the findings, but the prospective study of 300 newly referred dyspeptics to a GI clinic has given considerable encouragement to the belief that a more rational system to define priority for investigation in dyspeptic patients may be available. The fact that the scoring system correctly identified all 7 early gastric cancers and 8 of 9 advanced gastric cancers as being high risk patients with a 9% false positive rate is directly comparable to the performance of a consultant gastroenterologist.

The value of this type of approach is not only in identifying priority for investigation but it may identify those

with so remote a chance of harbouring any serious pathology that the need for endoscopy could be avoided. Thus Mann et al (1983) and Davenport et al (1985) have speculated at least 30% of endoscopies could be avoided. Using the artificial cut-off derived in the retrospective group for low risk in the current study 20% of the 300 clinic referral patients could also in theory have had endoscopy withheld. Thus a scoring system has been produced which has more potential to accurately define risk of gastric cancer than that previously proposed by Gear and Barnes (1980). These authors suggested that new-onset dyspepsia of two weeks duration in middle age was sufficient evidence of risk to warrant endoscopy. This approach has been supported by Ward and Johnston (1986) in Leeds and by Fielding (Allum et al, 1986) in Birmingham. Since one percent of the population over 40 years of age fit this criterion of 'risk' (Gear and Barnes, 1980), 110,000 endoscopies would be required to be performed in the first year of screening if all individuals aged 40-65 years were thus considered and accepting a steady state of 0.4% entry per year, a further 44,000 endoscopies per year would follow (Gear and Barnes 1980). Allum et al (1986) have pursued this definition of 'risk' in a community screening service of new-onset dyspeptic subjects and gained a positive predictive yield for gastric cancer of 2.4%. They also found that there were a considerable number of follow-up endoscopies required in the further management of gastric ulcer and "premalignant" lesions such as chronic gastritis, intestinal metaplasia and dysplasia which would also accrue (Allum et al, 1986).

By trying to further define risk through symptom analyses the aim would be to define high risk and therefore accelerate investigation and at the same time reduce the number of unneccessary investigations. This would not increase the number of early gastric cancers found per year but would increase the yield per endoscopist should the system prove effective in a prospective manner. Thus the positive predictive yield for gastric cancer in the log likelihood ratio prospective study was 33% compared to 2.4% for the Birmingham study (Allum et al, 1986). The scoring system could perhaps render this form of selective screening more feasible particularly if the very low risk cases were simply observed following their first clinic visit.

For the present it would seem that there is no simple cheap and effective method to increase the detection of early gastric cancer or even advanced gastric cancer. Perhaps the British Society of Gastroenterologists' early gastric cancer/ dysplasia study will reveal much more about the natural history and symptomotology of these conditions that will permit their easier detection. However for the present perhaps as Cuschieri suggests instead of the ideal situation with endoscopy based in group practices, selective screening of such at risk groups as patients with Pernicious Anaemia may be necessary (Cuschieri, 1986).

In conclusion, multivariate aalyses as suggested by De Mello et al (1983) and Mann et al (1983) can be successfully applied to tumour markers and symptoms to identify cancer 'risk' in a symptomatic subject. However, neither will be as successful

alone as when both are combined.

Analyses of dyspeptic symptoms can define "risk' of gastric cancer including a high percentage of patients with early gastric cancer. This approach is worthy of further prospective study and is currently underway in two referral centres in West Yorkshire.

Chapter 5

Conclusions

Haemoccult detects asymptomatic colonic cancers and significant sized adenomatous polyps. The rate of three cancers identified per 1,000 individuals screened is comparable with other British studies and coupled with a predictive yield of 33% highlights the potential of this agent in population screening for colorectal cancer.

Fecatest has an unacceptably high positive rate (12.6%) even with adequate dietary restriction, whilst yielding no neoplastic disease on subsequent investigation of these cases. This precludes its use as a screening agent for colorectal cancer. Hema-chek seems in this limited study to be less sensitive to occult blood in the stool than Fecatest but would appear similar to Haemoccult and may be worth further examination in view of its slightly lower cost.

A self-administered symptom questionnaire can be designed to elicit gastrointestinal symptoms. However, a pilot study is mandatory to assess the validity of the responses attained, and should measure the acceptability of the questionnaire to the target population, as well as the consistency, reproducibilty and the applicability of the responses once recorded.

Screening for colorectal neoplasia with a symptom questionnaire did not reveal any unsuspected tumour, although many individuals with benign pathology were identified. The inclusion of a questionnaire can only lead therefore to an increase in the number of investigations performed and so increase the running costs of the screening programme.

Direct involvement of the GP in the initial screening approach during a routine consultation resulted in a 75% compliance rate. This rate was unaffected by age, sex or socio-economic factors. The response to a written invitation to attend the practice surgery to participate in screening was significatly less than for the direct approach at 50% ($p<0.05$). However, even this response is greater than the average compliance to a postal FOB method in the United Kingdom which is approximately 33%. These results would therefore seem to indicate that the way in which FOB screening is promoted is a critical factor influencing the final compliance rates and ultimately the viability of population screening.

There exist two distinct attitude profiles separating compliant and non-compliant individuals for a screening offer. Compliant subjects have good awareness of the benefits of the early detection and treatment of cancer, have a certain respect for the medical profession and feel that they may be potentially at risk from cancer. By contrast, the non-compliers are pessimistic about the treatment of cancer, hold the medical profession in low regard and have an unrealistic impression the impact illness makes on their lives. Psychologists and educationalists may be able to manipulate these attitudes in future studies to overcome resistance to screening and so increase the uptake of screening facilities.

The detection of symptomatic cancers with single tumour markers is poor even in relatively advanced cases. Similarly there is considerable overlap in the symptoms present in benign and

malignant GI disease. The application of multivariate analysis to the combination of symptom and tumour marker data showed a significant improvement in the diagnosis of GI cancer ($p< 0.02$), compared to either modality assessed on its own. Similarly the analysis of the dyspeptic patients' symptoms by the log likelihood method has shown itself to be of value in accurately predicting the probability of gastric cancer for a given individual. These approaches have the merits of being cheap, non-invasive and can rapidly identify priority for further investigation from within a sypmtomatic population, thereby having the potential to reduce the delays in diagnosis that can occur in general and hospital practice.

Future requirements for the earlier detection of colorectal and gastric cancer will depend on the development of more suitable diagnostic tests or selection of more appropriate 'at risk' groups. Immunological tests to identify only human blood with no cross-reactions with animal blood or preoxidases in food are currently being assessed and may make an impact on the false positive rate associated with FOB testing. The E-Z test which is a guaiac impregnated toilet paper may render FOB testing more acceptable to the population in future studies and so increase the cost-effectiveness of screening.

Further controlled studies of colorectal cancer screening with FOB's are required to determine the potential of this approach to reduce the mortality of this cancer. Included in these studies there should be scope to assimilate further data on factors affecting compliance, particularly the attitudes of non-

compliers to screening and the influence of any manipulations of these factors using educational pamphlets. The GP and the practice premises should become the pivot for any further large screening studies in this country as it has been repeatedly shown that his direct involvement in screening increases the compliance rate for most screening offers.

The earlier detection of cancer in the symptomatic population may be improved by the use of FOB tests in those individuals with lower GI symptoms to determine priority for investigation; for gastric cancer the results of the British Society of Gastroenterologists Early Gastric Cancer/ Dysplasia study may reveal certain discriminatory factors which will lead to the increased diagnosis of this condition.

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Appendix

Pilot questionnaire

THE DEPARTMENT OF SURGERY AT ST. JAMES'S HOSPITAL IN CONJUNCTION WITH LOCAL G.P.'s IS TRYING TO COMPOSE A SIMPLE FORM OF QUESTIONNAIRE WHICH WILL LEAD TO EARLIER DETECTION OF VARIOUS DISEASES

THE FOLLOWING QUESTIONNAIRE IS STILL ONLY A TRIAL ONE AND WE WOULD APPRECIATE YOUR HELP IN ASSESSING IT

COULD YOU PLEASE FILL IN THE QUESTIONNAIRE AS BEST YOU CAN, TAKING YOUR TIME AS THERE IS NO HURRY. IF YOU ARE NOT SURE OF ANYTHING OR THE QUESTIONS ARE NOT CLEAR, DO NOT ANSWER THAT QUESTION

ON COMPLETION OF THE QUESTIONNAIRE COULD YOU PLEASE TURN OVER ONTO THE BACK PAGE AND GIVE YOUR COMMENTS ON THE QUESTIONNAIRE, MENTIONING ALSO ANY PARTICULAR QUESTIONS THAT DO NOT SEEM CLEAR

PLEASE FILL IN A FEW PERSONAL DETAILS. ALL ANSWERS WILL BE ENTIRELY CONFIDENTIAL

NAME.....AGE.....SEX M/F
(FORENAME) (SURNAME)

ADDRESS ..... OCCUPATION (If you are unemployed or retired, please give former occupation)
.....
.....
.....
.....

THE FOLLOWING QUESTIONS PROVIDE USEFUL BACKGROUND KNOWLEDGE ON THE STATE OF YOUR PAST HEALTH AND YOUR FAMILY'S HEALTH

MOST QUESTIONS REQUIRE YOU TO PLACE A TICK IN THE CORRECT BOX OPPOSITE THE QUESTION

PAST HEALTH	YES	NO
HAVE YOU EVER ATTENDED A HOSPITAL OUTPATIENT CLINIC	[ ]	[ ]
HAVE YOU EVER BEEN A PATIENT IN HOSPITAL?	[ ]	[ ]

If YES to either question, please give a few details

.....

.....

HAVE YOU EVER HAD AN OPERATION ON YOUR STOMACH, BOWEL OR GALLBLADDER?	[ ]	[ ]
DO YOU HAVE SUGAR DIABETES?	[ ]	[ ]
DO YOU SUFFER FROM ARTHRITIS?	[ ]	[ ]
DO YOU SUFFER FROM ASTHMA?	[ ]	[ ]
ARE YOU BEING TREATED FOR RAISED BLOOD PRESSURE?	[ ]	[ ]

TREATMENT

DO YOU TAKE ANY MEDICINES/TABLETS REGULARLY?	[ ]	[ ]
ARE THESE FOR STOMACH OR BOWEL PROBLEMS?	[ ]	[ ]

If YES, please name them .....

.....

SMOKING AND DRINKING

Both smoking and drinking can affect your health. Please answer the following questions

DO YOU SMOKE?	[ ]	[ ]
HAVE YOU EVER SMOKED, BUT HAVE SINCE STOPPED?	[ ]	[ ]

PLEASE STATE AVERAGE AMOUNT SMOKED .....
(If you have given up, state average amount before stopping)

PLEASE RECORD AVERAGE ALCOHOL INTAKE .....

(e.g. 3 pints/night, 2 glasses wine/week)

FAMILY HISTORY

Some diseases run in the Family, e.g. Asthma, sugar diabetes

ARE THERE ANY DISEASES THAT RUN IN YOUR FAMILY?	[ ]	[ ]

If YES, please give details .....

.....

HAVE EITHER OF YOUR PARENTS OR BROTHERS OR SISTERS HAD AN OPERATION ON THEIR STOMACH, BOWEL, BREAST	[ ]	[ ]

If YES, please give details as best you can

.....

.....

THE FOLLOWING SECTIONS ARE RELATED TO YOUR HEALTH AT PRESENT
PLEASE TICK THE BOX THAT SEEMS MOST SUITED TO YOU
IF YOU ARE ASKED TO GIVE DETAILS TRY TO BE BRIEF

SECTION A	YES	NO
HAS YOUR APPETITE CHANGED RECENTLY?	[ ]	[ ]
If YES, has it DECREASED?	[ ]	[ ]
HAVE YOU LOST WEIGHT RECENTLY?	[ ]	[ ]
ARE YOU ON A DIET?	[ ]	[ ]
DO YOU HAVE DIFFICULTY SWALLOWING FOOD?	[ ]	[ ]
DO YOU FEEL THAT FOOD STICKS BEFORE REACHING YOUR STOMACH?	[ ]	[ ]
ARE YOU TROUBLED BY BURNING OR DISCOMFORT BEHIND THE BREAST BONE?	[ ]	[ ]
HAVE YOU EXPERIENCED ANY NAUSEA (feeling sick) OR VOMITING (being sick) RECENTLY?	[ ]	[ ]
DO YOU THINK YOU ARE EATING AS MUCH AS YOU WERE 6 MONTHS AGO?	[ ]	[ ]
DO YOU HAVE ANY PAIN OR DISCOMFORT IN THE ABDOMEN (Tummy) WHICH IS NEW FOR YOU?	[ ]	[ ]
IF YES, IS THIS DIFFERENT FROM PREVIOUS TUMMY UPSETS?	[ ]	[ ]

Please give details
.....

.....

SECTION B

A FEW QUESTIONS RELATED TO YOUR BOWEL HABIT NOW FOLLOW

HOW OFTEN DO YOU OPEN YOUR BOWELS (e.g. once alternate days).....		
DO YOU FEEL YOU EMPTY YOUR BOWELS ADEQUATELY MOST TIMES?	[ ]	[ ]
HAS THERE BEEN A RECENT CHANGE IN THE FREQUENCY OF YOUR MOTIONS?	[ ]	[ ]
HAS THERE BEEN A CHANGE IN THE APPEARANCE OF YOUR MOTIONS?	[ ]	[ ]
DO YOU HAVE EPISODES OF YOUR MOTIONS BEING LOOSE THEN BECOMING NORMAL AGAIN?	[ ]	[ ]
HAVE YOUR MOTIONS BECOME HARDER?	[ ]	[ ]
HAVE YOU NOTICED ANY BLOOD IN YOUR MOTIONS?	[ ]	[ ]
HAVE YOU EVER NOTICED SLIME IN YOUR MOTIONS?	[ ]	[ ]

SECTION C

THIS IS THE LAST SECTION TO BE COMPLETED. AS BEFORE PLACE A TICK IN THE APPROPRIATE BOX

	YES	NO
DO YOU HAVE A COUGH?	[ ]	[ ]
HAVE YOU EVER COUGHED UP BLOOD?	[ ]	[ ]
DO YOU SUFFER FROM PAIN OR DISCOMFORT IN YOUR CHEST?	[ ]	[ ]
DO YOU HAVE TO GET UP AT NIGHT TO PASS WATER?	[ ]	[ ]
If YES, IS THIS MORE OFTEN IN THE LAST SIX MONTHS?	[ ]	[ ]
DO YOU HAVE ANY DIFFICULTY PASSING WATER?	[ ]	[ ]
HAVE YOU EVER NOTICED BLOOD IN YOUR WATER?	[ ]	[ ]
HAS THERE BEEN ANY CHANGE IN COLOUR OF YOUR WATER RECENTLY?	[ ]	[ ]

If YES, PLEASE GIVE DETAILS .....

.....

.....

TO BE COMPLETED BY WOMEN ONLY

DO YOU STILL HAVE YOUR PERIODS	[ ]	[ ]
If NO, HAVE YOU NOTICED ANY BLOOD OR BROWN DISCHARGE FROM FRONT PASSAGE?	[ ]	[ ]

Study questionnaire

THE DEPARTMENT OF SURGERY AT ST. JAMES'S HOSPITAL IN CONJUNCTION WITH LOCAL G.P.'s IS TRYING TO COMPOSE A SIMPLE FORM OF QUESTIONNAIRE WHICH WILL LEAD TO EARLIER DETECTION OF VARIOUS DISEASES

COULD YOU PLEASE FILL IN THE QUESTIONNAIRE AS BEST YOU CAN, TAKING YOUR TIME AS THERE IS NO HURRY. IF YOU ARE NOT SURE OF ANYTHING OR THE QUESTIONS ARE NOT CLEAR, DO NOT ANSWER THAT QUESTION

PLEASE FILL IN A FEW PERSONAL DETAILS. ALL ANSWERS WILL BE ENTIRELY CONFIDENTIAL

NAME.....AGE.....SEX M/F
(FORENAME) (SURNAME)

ADDRESS.....OCCUPATION (If you are unemployed or retired, please give former occupation)

.....

.....

.....

.....

THE FOLLOWING QUESTIONS PROVIDE USEFUL BACKGROUND KNOWLEDGE ON THE STATE OF YOUR PAST HEALTH AND YOUR FAMILY'S HEALTH

MOST QUESTIONS REQUIRE YOU TO PLACE A TICK IN THE CORRECT BOX OPPOSITE THE QUESTION

PAST HEALTH	YES	NO
HAVE YOU EVER ATTENDED A HOSPITAL OUTPATIENT CLINIC?	[ ]	[ ]
HAVE YOU EVER BEEN A PATIENT IN HOSPITAL?	[ ]	[ ]

If YES to either question, please give a few details

.....

.....

HAVE YOU EVER HAD AN OPERATION ON YOUR STOMACH, BOWEL OR GALLBLADDER?	[ ]	[ ]
DO YOU HAVE SUGAR DIABETES?	[ ]	[ ]
DO YOU SUFFER FROM ARTHRITIS?	[ ]	[ ]
DO YOU SUFFER FROM ASTHMA?	[ ]	[ ]
ARE YOU BEING TREATED FOR RAISED BLOOD PRESSURE?	[ ]	[ ]

TREATMENT

DO YOU TAKE ANY MEDICINES/TABLETS REGULARLY?	[ ]	[ ]
ARE THESE FOR STOMACH OR BOWEL PROBLEMS?	[ ]	[ ]

If YES, please name them.....

.....

SMOKING AND DRINKING

Both smoking and drinking can affect your health. Please answer the following questions

DO YOU SMOKE?	[ ]	[ ]
HAVE YOU EVER SMOKED, BUT HAVE SINCE STOPPED	[ ]	[ ]

PLEASE STATE AVERAGE AMOUNT SMOKED.....
(If you have given up, state average amount before stopping)

PLEASE RECORD AVERAGE ALCOHOL INTAKE.....
(e.g. 3 pints/night, 2 glasses wine/week)

FAMILY HISTORY

Some diseases run in the Family, e.g. Asthma, sugar diabetes

ARE THERE ANY DISEASES THAT RUN IN YOUR FAMILY?	[ ]	[ ]

If YES, please give details.....

.....

HAVE EITHER OF YOUR PARENTS OR BROTHERS OR SISTERS HAD AN OPERATION ON THEIR STOMACH, BOWEL, BREAST? If YES, please give details as best you can	[ ]	[ ]

.....

.....

Please turn over

THE FOLLOWING SECTIONS ARE RELATED TO YOUR HEALTH AT PRESENT

PLEASE TICK THE BOX THAT SEEMS MOST SUITED TO YOU

IF YOU ARE ASKED TO GIVE DETAILS, TRY TO BE BRIEF

SECTION A	YES	NO
HAS YOUR APPETITE CHANGED RECENTLY?	[ ]	[ ]
If YES, has it DECREASED?	[ ]	[ ]
HAVE YOU LOST WEIGHT RECENTLY?	[ ]	[ ]
ARE YOU ON A DIET?	[ ]	[ ]
DO YOU HAVE DIFFICULTY SWALLOWING FOOD?	[ ]	[ ]
DO YOU FEEL THAT FOOD STICKS BEFORE REACHING YOUR STOMACH?	[ ]	[ ]
ARE YOU TROUBLED BY BURNING OR DISCOMFORT BEHIND THE BREAST BONE?	[ ]	[ ]
HAVE YOU EXPERIENCED ANY NAUSEA (feeling sick) OR VOMITING (being sick) RECENTLY?	[ ]	[ ]
DO YOU HAVE ANY PAIN OR DISCOMFORT IN THE ABDOMEN (Tummy)?	[ ]	[ ]
IF YES, IS THIS DIFFERENT FROM PREVIOUS TUMMY UPSETS?	[ ]	[ ]

Please give details.....

.....

SECTION B

A FEW QUESTIONS RELATED TO YOUR BOWEL HABIT NOW FOLLOW

HOW OFTEN DO YOU OPEN YOUR BOWELS (e.g. once alternate days).....		
AFTER YOU HAVE EMPTIED YOUR BOWELS DO YOU FEEL YOU STILL NEED TO GO?	[ ]	[ ]
HAS THERE BEEN A RECENT CHANGE IN THE FREQUENCY OF YOUR MOTIONS?	[ ]	[ ]
HAS THERE BEEN A CHANGE IN THE APPEARANCE OF YOUR MOTIONS?	[ ]	[ ]
DO YOU HAVE EPISODES OF YOUR MOTIONS BEING LOOSE THEN BECOMING NORMAL AGAIN?	[ ]	[ ]
HAVE YOUR MOTIONS BECOME MORE CONSTIPATED?	[ ]	[ ]
HAVE YOU NOTICED ANY BLOOD IN YOUR MOTIONS?	[ ]	[ ]
HAVE YOU EVER NOTICED SLIME IN YOUR MOTIONS?	[ ]	[ ]

Please turn over

SECTION C

THIS IS THE LAST SECTION TO BE COMPLETED. AS BEFORE PLACE A TICK IN THE APPROPRIATE BOX

	YES	NO
DO YOU HAVE A COUGH MOST DAYS?	[ ]	[ ]
HAVE YOU EVER COUGHED UP BLOOD?	[ ]	[ ]
DO YOU SUFFER FROM PAIN OR DISCOMFORT IN YOUR CHEST?	[ ]	[ ]
DO YOU HAVE TO GET UP AT NIGHT TO PASS WATER?	[ ]	[ ]
IF YES, IS THIS MORE OFTEN IN THE LAST SIX MONTHS?	[ ]	[ ]
DO YOU HAVE ANY DIFFICULTY PASSING WATER?	[ ]	[ ]
HAVE YOU EVER NOTICED BLOOD IN YOUR WATER?	[ ]	[ ]
HAS THERE BEEN ANY CHANGE IN COLOUR OF YOUR WATER RECENTLY?	[ ]	[ ]

If YES, please give details.....

.....

.....

TO BE COMPLETED BY WOMEN ONLY

DO YOU STILL HAVE YOUR PERIODS?	[ ]	[ ]
IF NO, HAVE YOU NOTICED ANY BLOOD OR BROWN DISCHARGE FROM FRONT PASSAGE?	[ ]	[ ]

Health Belief Model Questionnaire

In the following sections we would like you to read some statements about health problems, and indicate by circling one of the alternative answers how far you personally agree or disagree with the statement. There are no right or wrong answers; just give your opinion. Please circle ONE answer only for each question.

SECTION A

1. It is more important to have a good life now, than worry about future health.

6 (a) I completely agree
5 (b) I strongly agree
4 (c) I mildly agree
3 (d) I mildly disagree
2 (e) I strongly disagree
1 (f) I completely disagree

2. Physical fitness is important to me.

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

3. People can't really do a lot to prevent illness.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

4. Illness always gets me down.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

5. Fit people get as many illnesses as everyone else.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

6. I usually eat what I know is good for me.

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

7. Regular medical check-ups are useless unless you are ill.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

8. Good health or bad health is something you just have to put up with.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

9. I think that people are fanatical about health these days.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

10. Six monthly check-ups at the dentist are a waste of time.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

SECTION B

1. In general I enjoy good health

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

2. I am unlikely to suffer from a serious illness in the future.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

3. If I wait long enough, I will get over most illnesses by myself.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

4. I am the type of person who worries a lot about their health.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

5. I take ages to recover from illness.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

6. I go to the doctor the minute I feel unwell

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

7. I don't suffer from colds and flu as much as other people

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

8. I always have a well stocked medicine cabinet at home

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

9. I worry a lot about getting cancer

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

10. My health will probably always be below par

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

SECTION C

1. There is nothing I can do to prevent illness from happening

1	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

2. Finding a disease early makes no difference to the success of treatment

1	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

3. I am too old to worry about having health check-ups

1	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

4. A person can have a serious illness and not know it

6	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
1	(f) I completely disagree

5. Having a medical check-up usually stirs up trouble

1	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

6. I'd be frightened to have a check-up in case something was found

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

7. Certain medical tests can show up a problem you did not know about

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

8. I'd be prepared to give up my time if I could have a free medical check-up with my G.P.

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

9. There is no point in having a check-up if you have been well all your life.

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

10. Having a regular check-up for cancer is a good idea

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

SECTION D

1. I have great faith in modern medicine

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

2. Nurses and doctors always do what's best for you

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

3. I often feel confused after visiting the doctor

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

4. I can never see the doctor when I want

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

5. Doctors don't listen enough to their patients

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

6. It is important do <u>exactly</u> what the doctor says when I'm ill

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

7. There's a lot doctors don't know about most common illnesses

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

8. Doctors should spend more time telling their patients how to stay healthy

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

9. I don't like visiting hospitals

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

10. I worry about having to go into hospital

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

SECTION E

The next sections relate specifically to cancer. Your answers to the following statements are important as they will help us to make our cancer prevention programme more attractive to patients in our practice.

1. You can have cancer and not know about it

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

2. Finding cancer early leads to a better chance of cure

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

3. Tests can detect cancer before you feel unwell

6 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
1 (f) I completely disagree

4. No matter where you find cancer there is always a poor outcome

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

5. Cancer just about always means death

1 (a) I completely agree
(b) I strongly agree
(c) I mildly agree
(d) I mildly disagree
(e) I strongly disagree
6 (f) I completely disagree

6. The treatment for cancer is worse than the disease itself

	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

7. Having cancer is the worst thing that can happen to anyone

1	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

8. Some types of cancer can be cured more effectively than others

6	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
1	(f) I completely disagree

9. If I had cancer I would want to be told

6	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
1	(f) I completely disagree

10. If I thought I had cancer I would put off going to see the doctor about it

1	(a) I completely agree
	(b) I strongly agree
	(c) I mildly agree
	(d) I mildly disagree
	(e) I strongly disagree
6	(f) I completely disagree

This section asks in more detail about personal experience of cancer. If you have not known anyone with cancer, please proceed to Section F below.

1. Do you know anyone who has had cancer (a) Yes
(If the answer is no please proceed to the next section (b) No

2. Do you know anyone who has been cured of cancer (a) Yes
(b) No

3. Have you heard of either cancer of the stomach or bowel? (a) Yes
(If no please go on to the next Section below) (b) No

4. Has a relative or friend had either of these cancers? (a) Yes
(b) No

5. Did this greatly upset their way of life? (a) Yes
(b) No
(c) Don't know

6. Do you think you can have either of these cancers and not know it? (a) Yes
(b) No
(c) Don't know

7. Do you think the chances of cure for either of these cancers is (a) Good
(b) Fair
(c) Poor
(d) Don't know

SECTION F

Some illnesses prevent us leading our normal active lives. How much of an effect would the following illnesses have on your life.

Please tick the appropriate box for each illness

	Terrible effect	Large effect	Small effect	No effect
High blood pressure				
Heart attack				
Cancer				
Peptic ulcer				
Constipation				
Stroke				
Migraine				
Diabetes				

This is the last section. Please remember all your responses are strictly confidential and only your own doctor will see the answers. The information is necessary to help decide priorities for further health campaigns.

Please circle the appropriate answer as before.

Please state occupation.....
(If retired please stage last job)

Are you currently unemployed YES/NO

At what age did you leave full time education.....

Do you smoke? YES/NO

Have you ever had a previous health check-up? YES/NO

Ladies - have you ever had a cervical smear test? YES/NO

have you ever had a breast examination? YES/NO

Thank you for your co-operation. Could you now return the form in the stamped addressed envelope to the surgery?

Mood Scale From Pilot Study

N G This is the final Section.

Each of the words in the following list describes a way people sometimes Please use the list to describe how you have felt over the past two weeks, the table below.

e:

	Not at all	Seldom	Moderately	Quite often	Extremely
				✓	

indicate I've been angry quite often over the last 2 weeks.

he last two weeks I have felt

	Not at all	Seldom	Moderately	Quite often	Extremely
ess					
ensive					
ssed					
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JANGRT	AMDAHLV7	DISTCODE	SYSTEM
EMASTER	DATA	FILENAME	FILETYPE
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STANDARD		FORMS	

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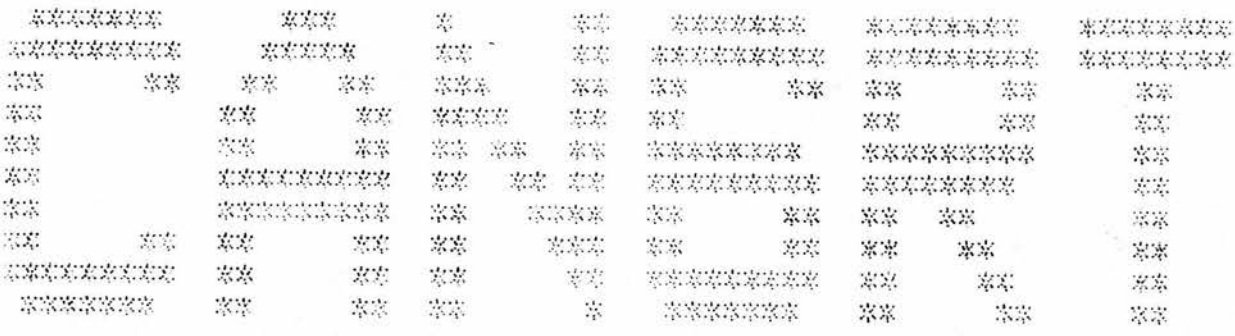

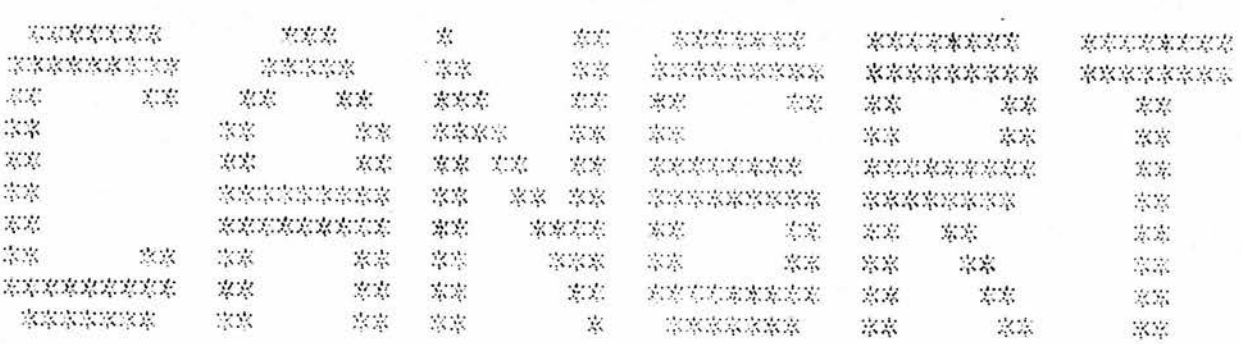

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EB005	0	66	0.72	2	2.5	8	YYNNNNNYYNYNYYNNNNNNNNNNONNNYNNNNNYYYYNNNN
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EB008	1	57	0.84	1	4.4	25	YYNNNNNYNYYNYNNNYNNYNYYNONNNNNNNNYNYYNNNN
EB009	0	58	0.84	1	3.3	7	YYNNYNNNNNYNYYYNNNNYNYNONYNNYYNNNYNNYNN
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EB012	0	52	0.91	1	2.5	35	YYNNYNNYNNYYYY NNYYYNNNONNNYYNNNNYNNNNNY
EB013	0	62	1.12	1	6.3	11	YYNNYNNN YYNYN NNNNNNNNONNNNNNNNNNNN NNNNN
EB014	0	60	0.72	1	6.3	13	YYNNNNNYNYYYYNNNNNNNNNYNONNYYNNNNNNYNNNNN
EB015	0	60	0.88	3	2.5	7	YYNNYYYYNNYYYN NNNNNNNNNONNNYNNNYNYYNNNNN
EB016	0	53	0.97	4	17.1	13	YYYNNNNYNYNYYNNNNN NNNNONNNYNNNNNNYNNNNN
EB017	0	51	0.68	2	15.8	61	YYNNNNNYYNYNYN NNNNNYYNONNNNNNNNYYNN NNNNN
EB018	0	50	0.68	1	3.6	11	YYNNNNNYNYYNNN NNNNNNYNONNNNNYNNNNN NNNY
EB019	0	47	0.80	1	8.0	12	YYNNNNNNNNYYNNN NNNYNNN ONNNNNNNNYNNN NNNNN
EB020	0	53	1.02	4	2.5	7	YYNNNNNYYYYYNYYYYYNYYNNNONNNYNNNYNNYNNNNN
EB021	0	50	0.74	0	9.4	70	YYNNNNNYNYYNNNNNNNNNNNN ONNNNNNYNNNN NNNNN
EB022	0	60	1.55	34	6.5	17	YYNNNYNYNNYNYYNNNNNNNYNNONNNNNYNNYYNNNNNN
EB023	1	53	0.92	4	6.0	27	YYNNNNNN YNYNN NNNNYNNNOYNYYNNNNNNNNNN
EB024	1	67	0.92	0	4.9	10	YYNYNNNYYY NNNNNNNNYNN ONNNNNNNYNNNNNN
EB025	1	59	0.87	3	2.5	7	YYNNNNYYNNNNNN NNNNYNN .NNNNYNNNNNYNNNN
EB026	0	56	0.74	0	8.7	10	YYYNNNNYNNNNYNNNNNYYYYNONNNYNNNYNYNNNNNNN
EB027	1	67	1.44	39	7.1	38	YYYNNNNN Y YNN NNNNYNN ONNNYNNNNNNN NNN
EB028	0	60	0.80	1	8.5	10	YYNNYYNYYY YNN NNNYYNNN1NNNNNNNNNNNYNNNNY
EB029	0	68	0.80	2	5.9	10	YNNNNNNNNNYNNN NNNNNNNNONNNNNNNNNNYNNNNN
EB030	0	56	0.90	0	4.4	58	YYNNNNYYNNNNYN NNNNYNN ONNNNNNNNNNN NNNNN
EB031	1	52	1.40	14	5.6	200	YYYNNNNNNNNYYNN YYNNNNNNNONNNNNNNNNNYYNNN
EB032	0	57	0.60	1	6.1	13	N NNNNNNNNNNYN NNNNNNN ONNNNNNNNNNN NNNNN
EB033	0	62	0.90	0	3.3	14	N NNNNNNNNNNYNNNNNNYNN .NYNYYNNNNNYNNNNNN
EB034	0	59	1.00	1	3.7	11	YYNNNNYYNNNNNYYNNYNNNNONNNYNNYYNNN NNNNN
EB035	0	60	0.62	2	10.4	14	YNNNNYNNNYN NNNNNNNNNNONNNNNNNYNNNNNNNNN
EB036	0	63	1.44	44	2.5	18	YYNNYNNNYNY YNN NNNYYYYYONNNNNNNYNNYNNNNNN
EB037	0	67	0.58	2	2.3	12	YYNNNNNNNNNYNNN NNNN NN ONNNNNNNNNNYNNNN
EB038	1	47	0.90	0	2.5	15	YYYNNNNN NYNYN NNNNNNNYNONNNYNNNNNNNNNN
EB039	1	57	0.90	1	6.8	12	YYNNYNNYNNNNYNNNNNNNNNN.N1NNNNNNYYNNNYNNNY
EB040	0	52	0.72	5	2.7	9	NYNNYNNYNY YYN NNNNNNN ONNNNNNNNYNNNYNNNNNN
EB041	0	51	0.76	1	2.5	12	YYNNNNNNYYY YNN YNNNYNN ONNNYNNNNNNYYNNNNN
EB042	0	62	1.04	3	3.0	35	YYY YY YYNNNNN NNNNNNNNNOYNNYNNNYNYYNNNN
EB043	0	59	1.18	10	9.5	11	YYYNNNYYNY NYN NNNNNNNNNONNNNYYNYNNYNNNNNN
EB044	1	45	1.00	8	6.1	19	YYYN YNYNYNYNN YYNNNNN ONNNNNNNYYYYNNNNN
EB045	0	54	0.96	3	2.5	19	YYNNNNNNNNNYNNNNNNNNNNNNNNONNNNNNNNNNYNNNNNN
EB046	0	63	0.90	0	3.6	18	YYNYNYNYNY YYN NYNNNNNNONNNNNNNNYNNN NNNNN
EB047	1	64	0.69	0	11.2	22	YYYNNNNNYNY NYN NNNNNNYNONNNYNNNNYNYYYNNN
EB048	1	64	0.82	0	2.5	12	YYNNNNNNNNNYNNN YYNNYNNNONNNNYYNNNYNNNN
EB049	0	50	0.86	0	2.3	7	YYNNYYNYNNYYNN NYNNNNNNNONNNNNNNNYNNYNNNNNN
EB050	1	54	0.71	3	2.5	9	YYYNNNYNYNYYNNNNNN NNN OYYYYNYNNNYYNYN
EB051	1	58	0.71	0	2.5	17	YYNNNNNYYYNNYYYNNNNNNNYYOYNNYNNNNNYYNNNN
EB051	1	60	0.55	0	2.5	24	YYNNNNNYYYNNYYYNNNNNNNYYOYNNYNNNNNYYNNNN
EB052	0	61	0.90	0	2.5	6	YYNNN YYNNNNNNNNYYNNNNNNNONNNNYYNNNNYNNNNN
EB053	0	50	0.77	0	5.7	6	YYNNYNNNNYNNYNNNNNNYNNNONNNYNNNNYNNNNN YY

AGP CRP CCA CGT

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	A	A	AGP	CRP	CCA	CGT	
EB054	0	60	0.82	0	2.5	7	YYYNNNNNNNNNYNNNNNNNNNNNNNONNNNNNNNYNNNNNNN
EB055	1	51	0.54	0	3.0	15	YYNNNNNNNNYNNNNNNNNNNNNNNONNNNNNNNYNNNNNN

B057	.	.	.	.	.	.	NYNYNNNNNNYNNNNNYNNNNNNNONNNNNNNNNNNNNNN	60
B058	1	52	1.19	6	2.9	20	YYNNYNNYNYNYNYNNNNNNNNNNNNONNNNNNNNNNNNN	60
B059	1	70	0.76	0	2.5	19	YYNNYNNYYYYNNNNNNNNNNNYNNNONNNNNNNNNNNYNNNN	60
B060	0	62	1.06	3	3.4	15	YNNNYNNYYYYNNYNNNNNNNNNNNNONNNNNNNNYNNY NNNNN	60
B061	0	66	0.71	0	2.5	31	YYNNNYNYYYNNNNNNNNNNNNNYNNONNNNNNNNNNNNYNNNNN	60
B062	1	61	1.00	1	2.5	10	YYNNNYNYYYYNNNNNNNNNNNNNNONNNYNNNNNNNNNNNN	60
B065	0	54	0.76	3	2.5	18	YYNNNNNNNNNYNNNNNNNNNYNNNNONNNNNYNNNNYNNNNNN	60
B066	1	64	0.76	0	2.5	12	NNNNNNNYNNNYNNNNNNNNNNNNNNONNNNNNNNNYYNNN	60
B067	0	50	0.76	2	2.5	23	YYNNNNNNNNNYNYNNNNNNNNNYYONNNNNNNNNNNNYNNNNN	60
B068	0	60	0.82	2	2.5	23	YNNNNNNNNNNYNYNNNNNNYNNNNONNNNYNNNNNYNNNNNN	60
B069	0	66	.	.	.	.	YYNNYNNNNNNNYNYYNNNNYNYNONNNNYNNNNNNYNYYNY	60
B071	0	55	.	.	.	.	NNNNNNNNNNYNNNNNNNNNNNNONNNNNYNNNYNNNNNYN	130
B072	0	58	0.73	1	.	6	.	.
B103	1	65	1.04	1	5.5	16	YYYNNNNNNNYNN NNNNNNNNYNNONNNNYNNNNNNNNN	60
B104	0	57	0.83	1	5.7	14	YYNNYNNYNYNNYNNNNNNNNYNNNNONNNNNNNNNYNYYNNNNN	60
B107	1	65	.	.	.	.	YYYNNNNNYYYNNYNNNNNNNNNNNONNNYNNNYNNNNNNNN	.
B108	0	61	.	.	.	.	YYNNNNYNYYYNNYNNNNYNNNNYYOYYNYNYNNNYYNNNNNN	60
B109	1	64	0.84	6	2.5	45	YYNNNNNNNNYNNNNNNNNNNNNNONNNNNNNNYNYNNNN	60
B110	0	59	0.84	3	3.0	15	YYNNYNNNNYNNNNNNNNNNNYNNNOYNNNYYNNNYNNNNNN	60
B114	0	60	0.73	1	3.9	17	YYNNYYNNNNNNNNNNNNNYYNNNNONNNNNNNNYNNYNNNNN	60
B121	1	62	0.84	3	3.7	12	Y NNNNNNNYYNNNNNNNNNNNNNONNNNNNNYNNNNNNN	60
B122	0	59	0.90	1	5.6	12	NYNNNNNNNYNNYNNNNNNNNNNNNONNNNNNNNNNNNNNN	60
B125	1	65	0.90	2	5.4	21	YYNNNNNNYYYNYYNNNNNNNNNYNONNNNNNNYNNYNNNN	60
B130	0	52	0.73	1	2.5	9	YNNNYNNNNYNYNNNNNNNNYNNNONNNNNNNNNNYNNNNN	60
B139	1	58	0.73	1	3.8	14	YYNNNNNNNNNYNYNNNNNNYNNNONNNNNNNNYNNNNNNN	60
B140	0	56	0.78	1	2.5	15	NNNNYNNNYNYNNYNNNNNNNNNNNNNOYNNNNNNNNNNNNN	60
B142	0	57	0.84	3	2.5	11	YYYNNNNNNNNNYNYNNNNNNNNNNNNONNNNNNNNNNNNNN	60
B156	0	51	0.78	4	2.5	9	YYNNNNNNYNNYYNNNNNNNNNNNYNONNNNNNNNNNNYNNNN	60
B164	0	62	0.83	1	3.2	10	YYYNNNNNYNYNNNNNNNNNNNNNNONNNNYNNNYYNNNNNNNY	60
B171	1	63	.	.	.	.	YYNNNNNNNNNNNYNNNNNNNNNNNNOYNN NNNNNNY NNN	60
B172	0	55	.	.	.	.	YNNNNNNNYYYNNYNNNNNNNNNYYYONNNYNNNNNNNYNNNNNN	60
B173	1	64	0.89	2	2.5	9	NYNNYNNNNNNNNNNNNNNNNYNNNONNNYNNNNNNNYNNNN	60
B174	0	60	0.59	1	6.0	22	NNNNYNNNYNYNNNNNNNNNNNNNNNNONNNNNNNNNNYNNNNNN	60
B177	1	62	0.72	2	2.6	8	NNNNNNNNNN NNNNNNNYYNYNNONNNNNNNNNNYNNNNN	130
B178	0	57	1.05	1	6.0	10	YYNNYNNNYNYNYNNNNNNNNNNNNNONNNNNNNNYNNYNNNNNY	260
B180	0	57	0.78	1	2.5	28	YYNNNYNNNNNNNYNNYYNNNNNNNNONNNNYNNNNNNNNNNN	60
B187	1	57	0.97	3	6.0	30	YYYNYYNYNYNNNNNNNNNNNNNNNONNNNNNNYNYNNNNN	60
B188	0	55	0.99	2	6.6	29	YYNNNNNYYYNN NNNNNNNNNNNONNNNNNNYNNYNNNNNN	60
B195	1	57	0.99	1	2.5	7	YYNYNNNYNNYYNNNNNYNNNNNNNONNNNNNNNNNYNNNN	60
B196	0	62	0.64	1	2.5	5	YYNNNN NNYNYNNNNNNNNNNNNNONNNNNNNNNNNNNNN	60
B197	1	60	1.10	5	.	9	YYYNYNNNNNYNNNNNNNNNNNYNYYONNYNNNNYNNNNNNN	60
B198	0	61	0.89	3	.	23	NYNNYNNNNYNNNNNNNNNNNNNNNNONNNNNNNNNYNNNNNN	60
B201	1	63	0.94	1	3.5	13	YNNNNNNNNYNNNNNNNNNNNNNNNONNNNNNNNNYNNNN	60
B202	0	65	1.05	1	6.4	9	YNNNYNNNNYNNYNNNNNNNNNNNNNONNNNNNNNNNNNNNN	60
B204	0	65	0.68	3	2.5	12	YYNNYNNNNNYYNNNNNNNNYNNNONNNNNNNNNYNNNNNNN	260
B207	1	63	1.00	4	2.5	19	YYNNNNNNNYNNNNNNNNNNNNNNOYNNNNNNNNNNNNNN	130
B208	0	61	0.86	3	4.8	8	YYYNNNNYYYNNNYYNNNNNNNNNOYNNYNNNNNNNNNNNN	130
B209	1	69	1.00	3	2.9	15	Y NNNNNNNNYNNNNNNNNNNNNNNONNNNNNNNNNNNNN	60
B210	0	62	0.72	12	2.5	16	YYNNYNNNNNNNNYNNNNNNYNNNONNNNNNNNNNYNNNNNN	60
B213	1	56	.	.	.	.	NY NNNNNNNNNNNNN NNNNNNONNNNNNNNNNNNNN	130
B214	0	53	0.94	5	.	8	YYNNNNNNYNNNNNNNNNYNNNNNNNNONNNNNNNNNNNNNNN	130
B217	1	61	1.74	2	5.2	9	YYN NNNNNYNNNNNNNNNNYYNONNNNNNYYNYYYYNN	.

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B224	0	47	1.05	4	.	22	YYNNNYYYNYNYNNNNNNNNYYYONNNNNNNNYYNYNNNNNN	130
B226	0	57	0.51	42	7.1	9	YYNNNNNNNNNYNYNNNNNNNNNNNNONNNNNNNNYNYYNNNNN	260

EB227	1	53	0.77	2	.	26	YYNNYNNYNNN

ED019	0	80	0.83	4	4.6	240	YYYYYYYYYYYYYYYYYYYYYYY OYYYYYYYYYYYYYYYN
ED020	0	54	1.00	3	5.4	22	YYYNYNNYNNYYYN NNNNNYYYOYYYYNYNNNYN NNYNI
ED021	0	63	0.83	1	6.7	62	YYNNYNNYYN NYN YY YYYYNONNNNNNNNNN YNNNNN
ED022	1	57	0.73	1	3.7	12	YYYYNNNYNNNNNN NYNNNYN ONNNNNYNN NN NNN
ED023	1	62	0.68	1	3.2	13	Y NNNNNNNNYNNYYNNNNNYYNONNNYYNNNNNYYNNY
ED024	0	71	1.23	4	6.5	35	NYYNYNNYYNY N NNYYYYN OYNNY NNNNNYYNNNN
ED025	0	84	0.89	4	3.9	10	NYNNNN YNNYYYNNNNN YYN ONYYNNNNNNNYNNNNN
ED026	0	69	1.69	66	5.2	37	YYNNNNNYNY NYYYYNNNNYN OYYYNYNNNNNN NNNNI
ED027	0	67	1.11	30	6.4	902	YYYYN YYNYYYN YYNYYYYYOYNNNNNNN YYNNYNI
ED029	0	24	0.40	4	3.2	10	NYNNNYNYNNNYYYYYNNNNYYYON NNNNNN NNYY
ED032	0	56	1.17	11	3.7	25	YYNNNNYYNNYYYYYYNNNNYN ONYYNNNNNNNYYNNYN
ED033	0	40	0.73	1	4.2	18	YYYNNNNYYYYYYYYYNYYYYN1YNYYYYYYNYYYNNYY
ED034	0	40	0.68	1	2.5	10	YYNNNNNN NYNYN NNNNNY NOYYYYNNNYNNYNNNNY
ED035	0	71	0.92	0	4.0	11	YYNNYNNYNY NYNNYNNNYN YOYYYNYYNYYNYNNNNNI
ED036	0	68	1.17	1	11.7	12	YYYNNYNYNNYYNNNNYNNYN YONYNYYYNYNNYNNNNNI
ED037	1	49	0.99	1	2.5	73	YYYNYNNN NNYYNNYNNNNY Y1NNYNYYNNNNNNNNY
ED038	0	78	0.83	4	2.5	10	YYNNYNNYNNNNNNNNNNNNNNNNOYNNNNYYNNNNNNNNI
ED039	0	36	1.29	1	7.2	32	YYYNNNNYNYNYYYYNN YYYYNOYYYYNYY YYYY YNNNI
ED040	1	46	1.42	13	4.8	39	YYNNNNNYYYYNNNNNNNNYYYNONNNNNNNNNNYNNNN
ED041	1	50	0.73	1	2.6	16	YYNNNNNYYYYYNNNNNNNNN YONNNYNNNNNNYYNNN
ED042	0	80	0.83	1	2.5	10	YYYNYNNYNNN YNYYN Y ONYNYNNYNNNY NNN
ED043	1	49	0.78	1	2.5	19	YYYNNNNYYNY NNNNNNYY NONNNYNYYNNNYNNNN
ED044	1	21	0.73	1	2.5	10	YYNNNNNN N NNNNNNYYYN NOYNNNNNNNNYN NNN
ED045	0	.	2.61	157	4.7	26	YYY YYNNYYYNNNNY YONNNNNNNNNNNNNNNNI
ED046	1	69	0.83	1	2.5	10	YYYNYNN NY NN YYN NN ONNNNNNNNNNY NNN
ED047	1	73	0.80	1	3.1	7	YYNNNNNNNNNYNNNN NNYYNN NONNNNYNYNNNYYNNN
ED048	0	36	0.50	1	2.5	8	YYNNNNNY NNNNYNYNNNNY 1YNNNYNNNNNYNNNYYI
ED049	0	.	0.00	1	2.7	6	.
ED050	1	26	0.96	1	3.3	11	YYNNNNNNNNYYNNYYNNYNNY YONY YNNNNNNNNNNY
ED050	1	26	0.96	1	3.3	11	YYNNNNNN Y NNYYNNYNNYYYONY YNNNNNNNNNNY
ED051	0	50	1.05	1	2.5	13	YYYNNNYYNNNN NNNYNNNY Y1YYYYNNNNNNYNNNNNI
ED052	0	74	1.09	1	3.3	13	YYY YNNNNNNYYYNNNNN N1YNNNNNNNNNN NNNNI
ED053	0	59	0.98	1	2.7	25	YYYNYNYY NNNNYYNNNNY YONNYNYYNNNYYNNYNI
ED054	0	27	0.81	1	2.5	11	YYYNNNNYYNYYNYYYNNNNY Y1YYNNYNYNNNYYNNYY
ED055	.	.	0.94	11	2.5	135	.
ED056	1	55	1.06	3	3.5	31	YYYNNNNN YY YN NNNNNN N1NNNNNNNNNNNN NNN
ED057	0	54	0.98	1	4.7	15	YYYN NNY NYNYYNNNNNNN NONNNNYNNNNNNNNNNNI
ED058	1	41	0.89	1	4.0	8	YYNNNNNNNNYNYNYYYNYYYNNNONNYNNYNNNYYNNNN
ED059	0	55	1.06	1	7.8	8	YY NNNNYNYYNYNNNNNNNN YOYYYNNNYYNYYNNNNNI
ED060	0	63	0.98	1	2.5	9	YYNNNNNN NYNNN NNNNNN YOYNNNYNNNNYYNNN
ED061	0	68	1.11	1	3.5	25	YYYNNNNYYNYNYYYYNNNNN YONNNNNNNNNNYYYNNNNI
ED062	0	69	1.06	1	2.5	10	YYYNYNNN NNNN YNN NN YONNNNNNNNNNYYNNNNI
ED064	1	51	0.89	1	1.6	10	YYYNNNNN Y NNN NNNNNY YOYNYNYNNNNNYNYNN
ED065	0	24	0.85	1	2.5	6	YYNNNNNNNNNNYYYYYNNNNY Y1YYYYYYYNNNNNYNYI
ED066	1	48	1.06	3	2.5	16	YYYNNNNNNNNYNNNNYNNNNN NONNNNNNNNNNNYNNN
ED067	0	23	0.81	1	2.5	10	YYYNNNNNNNY YNYYYYNNNN N1NNNYNYNNNNNNNNNY
ED068	0	68	1.06	3	2.5	9	Y YNNNNNNNNYNNNNNNYYNYYNONNYNNNN
ED069	0	74	1.03	1	2.8	27	YYNNYNNYNNNNNNNNNNNNNYNNN1NYYYNYNYNNYYNNNNN
ED070	1	52	0.57	1	2.5	13	NNNNNNNNNNNNNNNNNNNNNNNNNNONNNNYYYNNNNNNN
ED071	0	30	1.14	1	2.5	8	YYYY N NNYYYYYNNNNNY YONY Y YNNYYYNNNNNN
ED072	0	76	1.68	1	4.5	26	YYNNYNNYNNNNYNNNNNNYNNNONNYNNYYYNNNNNNNN

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ED073	0	73	1.14	1	5.4	14	YYYNYNNNNNN YYYYNNYY YONNNYNNNNNNNNNNNN
ED074	0	23	2.75	43	3.8	33	YYYNNNNYYNYNNYYYNNNNY Y1NNNNNNNNNNN NNNY

ED075	0	30	0.47	2	2.6	6	YNNNNNYNNNNN

ED135	.	52	1.06	3	2.5	32	YYNNNNNNNNNYNNNNYYNNYNYNONYNNYNNYNYNNNNY
ED136	0	72	1.26	7	3.9	34	YYNNYNNY NYNYYYYNNNNYYYYONNNNYNNNNYYNNNN
ED137	1	24	0.94	6	3.5	14	YYNNNNNYYYNNNNNNNNNYYNNONNNYNNNYNNNNNNN
ED138	0	41	.	.	.	.	YYNNNNNNNNYNNYYY NNNNYYY1YNYYYNYYNNNNNY
ED139	0	26	.	.	.	.	YYNNNNNYYYYNYNYYYNNNNYYNONYYYNNNNNNNNNN
ED140	0	55	.	.	.	.	YY NNNNYYNNNYNNYYNYYNNNONNNNNNNNNYNNNNNN
ED141	0	30	0.65	1	2.5	17	YYNNNNNNNNYNNNNNNNNNNNYY1YNNNYNNNNNYNYNN
ED142	0	.	1.26	3	2.5	13	YYNYNNYYYNYNYNNNNYNNNNNNONNNNNNNNNNYNNN
ED143	0	64	0.82	0	2.6	20	YYYNNNNNYNNNNYNNNNNNNNYYN1NNNYNNNNNYNNNNN
ED144	1	80	1.00	9	2.5	38	YYNNYNNYNNYNNNNNNNNNNNNNN.NNYYNYYNNNYNNNN
ED145	1	46	1.04	2	4.6	18	YYYNNNNNYNYNNY NNN YYYONNNNNNNNNNNNNNNN
ED146	0	51	0.83	1	2.5	11	YYYNNNNNYYYNNNYYYNNNNNYYYONNNNNNNNNNNNNNN
ED147	1	21	1.19	1	3.5	13	YYNNNNNNYYYNNNYYNNNNNNYYYONNNNNNNN
ED148	0	63	1.50	3	3.2	13	YYNNNNNYYNYNNNYYYYN NNYYYONNNNNNNNNNYYNNNN
ED149	1	65	1.19	3	4.8	16	YYNNNNNNYYYNNNNYYNNNNNNYYYONNNNNNNNNYNNYNNNN
ED150	0	45	0.83	2	3.2	9	NNN NNNNYNNNNYYNNNNNNONN Y NNNNNNNNNYY
ED151	0	40	0.90	1	5.1	7	YYNN NNNNYNYYYY NNNNYYY1 Y N NYNNYNNNNYY
ED152	0	19	0.83	1	2.5	6	Y NNNNNNYYNYNNNYYNNNNNNNYYONNNNNNNNNNNNYNNNNY
ED153	0	64	1.50	5	4.5	47	YYYNYNNNNNNYNY YNNNYNNONYYYYYYNYNYYNNNNN
ED154	0	42	0.90	5	6.2	13	YY NNNNYNYNYYYYNNNNNNYY 1YNYNNNYYYNYNNNNNY
ED155	0	64	0.63	3	5.2	17	.
ED156	1	46	0.83	1	2.5	9	YYNNNNNNYYYNNNNYYNNNNNNYYYONNNNNNYNNNNYNNNN
ED156	1	46	0.83	1	2.5	9	YYNNNNNNYYYNNNNYYNNNNNNNYYONNNNNNNNNNNNNNNN .
ED157	0	.	0.83	3	2.5	10	.
ED158	0	57	1.19	4	4.9	12	YYYNNNNNYNYNYNNNNNNNNNYYNONNYYNNYYNNYYNNNNN
ED159	0	50	0.83	1	2.5	11	YYNNNNNNYYNNNNNNNNNNNNNNYYOYNNNYYNNNNYNNNNN
ED160	0	46	1.04	2	2.8	14	YYNNNNNNNNYNNNNNNNNNNNNNNNONNNNNNNNNNNYNNNNY
ED161	0	57	0.90	1	9.1	12	YYYNNNNNYYYNNNYYYNYYNYY OYNNNNNNNNYYYNNNNN
ED162	0	57	0.51	3	2.5	16	YYNNNYNYYYNYNNYNYNN YYYO YNYNNN NNNNNNN
ED163	0	61	0.97	5	4.0	21	YYNNNYNNYYNYNNNYYYNNN NYYOYYYYNNNNNNNYYNNNN
ED163	0	61	0.97	5	4.0	21	YYNNNNNNNNNNNNNYYYNNNNNYYONNNYNNNYNNNNNNNNN
ED164	1	66	0.76	1	2.5	30	YYYNNNNYYNNNNYYYYYYYYYYNONNNYNNNNYYNNNNN
ED165	1	68	0.76	1	2.5	30	YNYNNNNYYYNNNNNNY NYYYYYONNNYNNYNNYYNNNN
ED166	1	81	0.97	1	6.6	30	YYYNNNNYYNNNNNNNNNNNNYNYNONNNYNNNYNNYYNNN
ED167	1	70	1.04	1	2.5	30	YYYNNNNNNNYNNNNYYNNNNNYYYONNNNYNNNNNYYNNN
ED169	0	55	0.66	3	5.5	28	YYYNNNNN YNNNNNNNNNNNNNNONNNNNNNNYNNYNNNNN
ED170	1	70	1.44	6	4.8	11	YYNNNNNNYYYNNNNYYNNNNNYNYN.YNNNNNNNYNNYNNNY
ED171	0	50	0.78	3	2.6	17	YYNNNNNNYYYNNNNNNYNNNNNNNNONNNNNNNNNNNYNNNN
ED172	0	22	0.83	1	2.5	8	YYNNNNYNNNNNNYNNNNNNNYYYYY1YNNYNYNYYYYYNNNY
ED173	0	49	0.59	1	2.5	8	YYNNNNNNNNNNNNNNNNNNYY YYONNNYNNNYNYY NNNY
ED174	0	65	0.89	1	6.4	11	NYYNY YYNNNNNNNNNY YNYNOYNNYNNYYNYYNNNNNN
ED175	1	72	1.10	21	3.9	22	YYNNNNNNYYNYNNNNNNNNNNNNYYOYYYNNNYYNNYYNNN
ED176	1	72	1.72	51	2.5	36	YNNNNNNNNNNNNNNNNNNNNNNNNN1NYYYNNNYNNYYNNN
ED177	1	50	0.89	1	2.5	10	YYNNNNNNYYYNNNNYYNNNNYNYYONNNNNNNNYNNYNNNN
ED178	0	42	0.73	1	2.5	6	YYNNNNNNNNNNNNNNNNNNNNYNNNONNNNNNNNNNNNNNNY
ED179	1	33	0.89	1	2.5	53	YYNNNNNNYYYNNNNNNNNNNNNYYYONNNNNNNNNNNNNNN
ED180	0	66	1.16	2	2.5	14	YYNNNNNYYNNYNNNNNYNNNNNNNNONNNYNNNNNNYYNNNN
ED181	1	59	.	.	.	.	YYYNYNYYYYNNNNNNYYNNNNNNNONYYYYYYNNNYYNYY
ED182	0	78	.	.	.	.	Y NNNNYYNNNNNNNNNN YY1 YYY NY
ED183	1	67	.	.	.	.	YYNNNNNNNNYNNNYNNNNNNNNNNNONNNNNYNNNNYNNNN
ED183	1	.	.	.	.	.	NNNNNNNNNNYYNNNYYYNNYYYYYX1NNYNNYYYNYNNNNNX
EL001	1	60	1.11	3	3.7	13	YYNNNNNYNYNYYNNNNNNNYNNNONNNYNYNNNYNNNNN

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EL002	0	50	1.77	14	2.5	11	YY NYNNYNNNYYNNYNNNNNNNO NNNNNNNNNYNNNNN
EL003	1	57	0.98	3	2.5	3	NNNNNNYNNNYNNNNYYNNNNNNONNNNYNNNNNYYNNN

EL005	1	62	0.49	1	2.5	15	YYNNNNNNNNNYNYNNNNNNNYNNNONNNYNNNNNNYNNNN	6C
EL006	1	56	0.78	6	2.5	14	YYNNYNNYNNNNNNNNNNNNNNNNNNONNNNNNNNNYNNNN	6C
EL007	0	56	0.66	3	2.5	9	YYNNNNNNNNNNNYNNNNNNNNNNNNONNNNYNNNNNYNNNNN	6C
EL008	1	58	.	.	.	.	YNNYNNNYNNYYNNNYYYNY NNONNNYNNNNNNYNNNNN	6C
EL009	0	57	0.94	1	2.5	8	NNNNYNYYNNYNNNNNNNNNNNNNNONNNYNNNNNNNNNNNN	6C
EL010	0	50	0.89	1	3.0	27	YYNNNNNNNNNNYNNNNNNNNNNNNONNNNNNNNNNYNNNNYN	6C
EL011	0	58	0.65	1	2.6	9	NYNNNNNNYNYNYYNNNNNNNNNNN1NNNNNNNNNNYNNNNNN	6C
EL012	0	65	0.52	1	3.2	9	YYNNNNNNYNNYYNNNNYNNNNNNNONNNNYNNNNNYNNNNNN	6C
EL012	0	65	0.52	1	3.2	9	YYNNNNNYYYNNYYNNNNNNNNNNNNONNNNNYYNNYYNNNNN	13C
EL013	1	60	0.89	1	2.5	10	YYNNNNNNNNYNYNNNNYNNNNNNNONNNNNNNNNNYNNNN	13C
EL014	0	57	0.74	1	2.3	9	YYNNNNNNNNNNNNNNNNNNNNNNNONNNYNNNNNNYNNNNNN	6C
EL015	1	67	1.04	1	3.8	8	YYNNYNNNNYNNNNNNNNNNNNNNNNNNNNNNNNYNNNNN	11
EL016	1	57	1.04	1	3.4	8	YYYNNNNNNNNYNYNNNNNNNNNNNNONNNNNNNNNNYNYNN	6C
EL017	0	50	0.89	1	2.5	4	YNNNNNNNNNNYNNNNNNNNNNNNNONNNNNNNNNNYNNNNN	6C
EL018	0	52	0.79	1	4.2	12	YYNNNNNNYNNNYNNNNNNNNNNN1NNNYNYYNNNNNNNNNN	6C
EL019	0	46	1.14	6	2.8	8	YYNNYNNYNNNNNNNNNNNNNYYNNOYNNYYNNNNNNNNNYN	6C
EL020	0	57	0.78	1	3.0	7	YYYN YNYNNYYNNNYYNNYNNNONNNYNNNNNNNYNNNNN	C
EL021	1	61	0.74	1	2.5	14	YNNNNNYYNNNNNYNNNNNNNNNNNNOYNNYYYNNNNNNNN	6C
EL022	0	68	1.19	1	2.5	10	YY N NYYNYNNNYNYYNNNNNNNONNNNNNNNNNYNNNNN	C
EL023	1	56	0.81	1	2.5	21	NNNNNNNNNNNYNNNNYYNNNNNNNONNNNNNNNNNYNNNN	C
EL024	1	65	0.91	11	3.2	10	YYNNNNNNNNYNNNNNNNNNNNNNNONNNNNNNNNNYYNNYN	6C
EL025	0	50	1.19	1	3.3	55	NNNNNNNNNNYNNYNNNNNNNNNNNONNNNNNNNNNNNNNYN	C
EL026	0	63	0.91	1	8.6	12	YYNNNNNNYNYNNNNNYNNNNNNN.NNYNYNNYNNYNNNNNN	C
EL027	0	64	0.91	1	2.5	6	NYYNYNNNNNNNNNYNNNNNNNYNNNONNNNNNYNNNNYNNNN	6C
EL028	1	53	1.07	1	2.5	10	NNNNNNYNNNNNNNNNNNNNNNNNNNONNNNNNNNNNYNNNN	6C
EL029	1	50	0.91	1	2.5	7	YYNNNNNNNYNNYNNNNNNNNNNNNONNNNNNNNNNNNNNN	13C
EL030	0	60	1.02	1	2.9	6	YYNNYNNNYYNNYNNNNNNNNYYYYOYYNNYNNNNNYYNNNNN	6C
EL031	1	52	1.07	8	2.5	23	YYNNNNNNNNNYNYNNNNNNNNNNNONNNYNNNNNYYNNNN	13C
EL032	1	63	0.63	4	2.7	14	YYYNNNYNYNNYNNNNNNNNNNNNNONNNYNNNYNNNNNNN	13C
EL033	0	60	0.90	6	4.5	27	YYNNY YYYNNYNNNNNNNNNNNNOYYNYNNNNNNYYNNNNN	6C
EL034	0	59	0.80	4	3.7	18	YYNN NNNNNYNNNNNNNNNNNNNNONNNYNNNNNNYYNNNN	6C
EL035	1	62	.	.	.	.	NYNNNNYYNYNNNNNNNNNNNNNNNONNNYNNNNNNNYNNYN	6C
EL036	0	54	0.90	5	9.7	17	YYNNNNNNNNNNNNNNNNNNNNNN1NNNNNNNYYYYNNNNNN	6C
EL037	1	62	.	.	5.7	.	YYNNNYNNYNNNNNNNNNNNNYNNNONNNYNYNNNNYYYNN	C
EL038	1	70	0.80	7	2.5	10	YYNNYNNNNNNNNNNNNNNNNNNNONNNNNNNN Y NNN	6C
EL039	0	50	0.93	5	2.5	4	YNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNYNNNNNNNN	6C
EL040	0	65	1.55	31	2.5	13	YYNNYNNNNYNNNYYNNNNNNNNNONNNNNNNNNNYNNNNN	13C
EL041	1	56	0.97	6	2.5	17	YYNNYNYYNNNNYNNNNNNNNNNONNYNNNNNYYNNNN	13C
EL042	0	55	0.50	1	2.5		YNNNNNNNNN YNNNNNNNNNNNOYNNNNNNNNNYYNNNNN	13C
EL043	1	62	0.65	13	3.4	47	YYNYNYNNNYNNNNNNNYNNNNNNONNNNNNNYNNYNNN	6C
EL044	1	60	1.02	4	2.5	17	YYNNNNYYNNYYNNNNNNNNYYYYNNOYNNYNNYYNYYNNN	6C
EL045	1	54	.	.	.	.	YYNNNNNNNNNNNYNNNNNNNNYNNONNNNNNNYNNYYYNYN	6C
EL046	0	67	1.44	6	2.5	10	NYNNNNNNNNNNNNNNNNNNN NNONNNNNNNNNNNYNNNNN	13C
EL047	0	61	0.80	1	8.7	19	NNNNNNNNNYYNNNNNNNNNNNNNONNNNNNNNNNNNNNNN	13C
EL048	0	63	0.90	2	6.2	11	YYYNYNNYNNNYNNNNNNNNNNNNONNNYNNNNNNNNNNN	11
EL049	1	66	0.80	2	4.9	20	YYNNNNNNYNNYNNNNNNNNNNNNNONNYNNNNNNNYNNNN	121
EL050	1	57	0.56	0	6.1	7	NNNNNNNNNNNNNYNNNNNNNNNNNNONYNNNNNNNNYNNNNN	6C
EL051	1	65	0.68	0	3.3	15	YYNNNNNN NNNNN NNNNNNN .NNNNNNNYYYYYNNN	6C
EL052	1	50	1.09	5	4.6	23	YYNNNNNNYNYYYNNNNNNNNYNNNONNNNNNNNNYNNNNNN	6C
EL053	0	63	0.72	4	5.2	9	YNNNNYYNNNNNN NNNNNNN ONNNNNNNNNNNN NNNNN	26C
EL054	1	58	1.19	24	5.3	61	YYNNNNNNYNNYNNYYYYNNNNN ONNYNYNNNNYYYNNY	26C
EL055	1	66	0.76	3	3.4	19	YYNNNNNNYNNNNNNYYYNNNYYYNOYNNYNNNNNYYNNNN	26C

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EL056	0	65	1.46	13	4.2	14	YYNNNNNNYNYYNNYYNNNNNYY DNNNNYNNNNNNN NNNNN	2
EL057	0	44	1.54	14	4.0	11	YNNNNNNNN NNNNYYYNNNNNNYYONYYYNNNNYNYYNNNNN	26C

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 0 62 0.64   1   2.7  18 YYNNNNNYYNNNNNN NNNNYNN ONNNNNNNNNNNYYNNNNNNN260
 1 67  .     .    .    . YYYYNNNNYYNYNNN NNNYYYYYNONNNNNNNNNYNNN NYN  260
 1 51 0.76   1   2.5   9 NYNNNNNNNNNYNNNNNNNNNNNYYYONNNNYYNNNNNNYNNNN 260
 1 70 0.72  10   4.0   7 YYYNNNNNNNNYYYYN NNNNNNNNNONNYYYNNNNNNYNNNNNN 260
 1 58 0.87   2   2.6  12 YNNNNNNNNNNNYNYN NNNNNNNN ONNNNYNYNNNNNYNNNN  260
 1 53 1.00   8   2.5  34 YYNNNNNYYNYYNYN NNNNYYYYYOYYYYNNNNYNYN NNN   260
 1 58 0.79   4   6.4  16 NYNNNNNNYNYYNYNNNNNNNNNN ONNNNNNNNYNYN NNN   260
 0 68 0.96  16   2.5  46 YYNNNNNN N NYYYNNNNNNYN ONNNNNNNNNNNYYNNNNNN260
 0 54 0.68   1   7.1  11 YNNNNNNNYNYNNYNNYYNNNNN ONNNNNNNNNYNYY NNNNN260
 0 70 0.92   1   3.2  43 YYNNNNYYNN YYN NNNYYNN ONNNNNYNYYNYYYNN  YY260
 0 71 1.09  10   2.5  20 YYNNNNNNYYNNNYNYYNNNNNNN OYNNNYNYNNYYNNNNNNN 60
 0 70 0.68   1   2.5  67 YY NYNYY NNYNN NNNNNNY ONNNNNNNNNNNYYNNNNN 60
 1 67 0.72   1   2.5  13 YYYNNNNNYNNYNNN NNNNNNN ONNNNNNNNYNNYNNNN   60
 0 50 1.05   5   5.4  19 YYNNNNNNNNYYYNYYYYNNYNYNONNNYNNNNNNNYNNNNNN 11  BP
 0 67 0.79   1   2.5  14 YYNNNNNNYYNNNYN NNNNNYN ONNNNNNNNNNNYYYNYNN 60
 1 65 0.64   1   2.5  25 YYNNNNNNYNNYYNN NYNNNNN ONNNNNYNNNNNYNNNN   60
 0 63 0.83   4   2.5  11 YYNNNNNYNNNYNYN NYNNYNN ONNNNNYNNNNNNYNNNNNN 60
 1 64 1.09   4   2.5  11 YNNNNNNNYNYNNNN NNNNNNN ONNNNNNNNNNNN N N   60
 1 60 0.72   1   2.5  15 YNNNYNNNYYNNNYN NNNNNNN. NYYYNYYNNNN NN     60
 1 60 0.72   1   2.5  15 YNNNYNNYYNNNYN NNNNNNN ONYYYNYYNNNN NNN     60
 0 60 0.92   1   2.5  11 YYNNYNNYNNNYYN NNNNNNN ONNNNNNNNNNNNNNNNN  60
 0 69 0.86   4   4.7   8 YYYNYNNYYNNNNNNNNNNNYNNNOYNNYNNNNNNN YNNNN 60
 1 59 0.47   3   2.5   8 YYNNNNNYNNNNNYNNYYNNNNNNONNNYNNNNNNYYNNNN   60
 0 68 0.65   2   5.7   6 NYNNYNYYNY NNNNNNNNNYNYYOYNNNNNNNYNNYNNNNNN 60
 0 51 0.77   3   2.6  41 YYN YNNYNY  NNNN NNNNNNONNNYNNN NNYNNNNYN 60
 0  .  0.86   8   2.5   8                                          .
 1 68 0.89   3   2.5   7 YYNNNNNNNNNYYNNNNNNNNNNNNONNNYNNNNNNNYYNNY   60
 0 56 0.86   3   5.6   8 YYNNYNNNNY YNNNNNNNNNNNNONNNNNYNNNNNNNNNNN 60
 1 69 0.60   1   2.5  35 YYYNNNNYYNNNYNNNNNNYNNNONNNNNNNNNNNNYNN    60
 1 69 1.47  12   2.5  16 YYNNNNNYYNYNYNNNNNNYNNYONNNNNNNNNNNNNNN   60
 0 62 1.00   5   2.5  15 YYYN  YYNY NYNNNNNNYNNNONNYNYNNYNNYNNNNNN 60
 0 62 1.06   9   2.5  18 YYNNNNNNNNNYNYNNNNNNNNNNONNNNYNNNNNNYNNNNY 60
 0 64 0.82   1   3.5  13 YNNNYNNYYNNYNNNNNNNNNNYNONNNNYNYNNNYNNNNNN 60
 0 60 0.71   1   2.5   5 YYNNYNNYNNNNNNNNNNYNYNNNONNNYNNNNNNNYNNNNNN 60
 1 70 0.82   1  13.2  13 YYNNNNNYNNYYNNNNNNNNNNNONNNNYNNNNNNYYYY    60
 0 68 0.82   3   2.5  27 YYNNNNNYYNNNYNNNNYNNNNNOYNNYNNNYNNYYYNNNNN 60
 1 52 1.00   3   2.5  15 YYNNYNNYYY NNNNNNNNNYNYNONNNNNYYNNNNNNNNN  60
 0 53 1.00   1   4.5  11 YYNNYNNYNYNNYNNYNNNYYYNONNNYNNNNNNNYNNNNY  60
 0 60 0.89   1   2.5  14 YYNNYNNNNNNYYNNNNNNNNNNONNNNYNNNNNYNNNNN  60
 0 69 0.94   1   2.4   8 YYNNNNYYNNNNYNNNNNNNNNNNONNNNNNNNNNNNNNNN 60
 0 51 0.83   4   2.5   9 YNNNNNNNYYNYYNNNNNNNNNNNONNNNNNNNNNNNYNNNNY 60
 0 56 0.97   3   3.8   9 YYNNNNNNNNNYYYNNNNYNYNNNONNNNNNNNNNNNNNNNN 60  DC
 1 68 1.11   3   3.5  17 YYNNNNNYNNYNNYYYNNNNNNNNONNNNNYYNNNYYYYNN   60
 1 54 0.97   3   2.5   7                                          .
 1 53 1.27   3   2.5  13 YYNNNNYYNNNNNNNNNNNNYNNNONNNNNNNNNNNYNNNN  60
 0 48 0.57   3   2.5   5 NYNNYNNNNNNNNNNNNYNNNNNYYONNYNYNNNNNNNNNNY 60
 .  .  .     .    .    . YYNNNNNYYNNNNYNNNNNNNNNNNNONNNNNNNNNNNYNNNN 60
 1 64 0.84   5   5.1  13                                          .
 0 62 0.84   3   7.4   9 YYNNYNNYNYNNYNNNNNNNNNNNNONNNNNNNNYNNYNNNNNN 60
 1 63 0.96   3   4.3  11 YYNNNNNNYYNYYNNNNNYNNYNNNONNNNNNNNNNNNNNNN  60
 0 64 1.09   4   3.3  12 YNNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNNNNNN 60
 1 66 0.84   3   4.2  21 YNNNNNYYNNYNNNNNNNNNNNNNONNNNYNNNNYYYNNNN   60
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 0 62 0.77   2   3.1  10 YYNNNNNNNNNNNNNNNNNNNNNNONNNYNNNNNNNNNNNN 60
 0 54 1.09   4   3.3  12 YYNNNNNNNNNNYNNNNNNNNNNYNONNNNNNNNNNNNNNNN 60
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223	1	61	0.84	2	5.2	15		
222	0	58	0.78	3	2.5	10	YNNNNYNNNNYNNNNNNNNNNNNONNNNNNNNNNNNNNNN	60
226	0	55	1.09	3	2.5	14	YYNNNNNNNNNNNNNNNNNNNNNN1NYYNNNYNNNYNNNNNN	60
227	1	63	0.84	3	6.7	30	YYNNNNNNNNYNNYNNNNNNNNNNNONNNNNNNYNNYNNNN	60
228	0	59	0.78	3	2.5	19	YYYNNNNNNNNYYNNNNNNNNYNNNONNNNNNNNNNNNYNNNNN	60
229	1	65	.	.	.	.	NNNNNNNNNNYNNNNNNNNNNNNNNONNNNNNNNNNNYNNNN	60
230	0	60	0.99	1	2.5	14	YYNNNYNNNNYNYNNNNNNNNNNNNONNNNNNNNNNNYYNNNNN	60
235	1	57	0.96	1	2.5	12	YYNNNNNNNNNNNYNNNNNNNNNNNONNNNNNNNNNNYNNNN	60
236	0	53	0.78	1	2.5	10	YYNNNNNNNNNYN NNNNNNNNYNNOYNNYYNNNNNYNNNNNN	60
237	1	56	0.78	1	2.5	22	YYNNNNNYYYNYNNNNNNNNNYNYNONNNYNNNNNNNNNNNN	60
238	0	54	0.84	3	3.1	29	YYYNYNYYYYNYYYNNNYNNNNYNONNNYNNNNNNNNNNNNNN	60
239	1	57	0.64	1	2.5	13	YNNNNNNNNNNYNNNNNNNNNYNNNONNNNNNNNNNNNNNNN	60
240	0	54	0.78	1	11.6	7	YYNNNYNNYNYNYNNNNNNNNNYYNONNNNNNNNYNYYNNNNN	60
241	1	56	0.78	1	2.5	21	YYNNNNNNNNYNNNNNNNNNNNNNONNNYNNNNNNNYNNNN	60
242	0	50	0.55	1	.	6	NNNYYN YNNYNNNNNN YNYNOYNNNNNNNNNYYNNNNY	60
243	1	55	0.78	3	2.5	21	NNNNNNNNNNNYNNNNNNNNNNNNONNNNNNNNNNNNNNNN	60
244	0	63	0.66	4	2.9	8	YYNNNNNYNYNNNNNNNNNNNNNONNNN NNNNYYNNNNN	60
245	1	54	0.72	3	2.6	17	NYNNNNYYNNNNYNNNNNNNNNNNNONNNNNNNNNNNNNNN	60
246	0	52	0.66	4	2.5	9	YYNNNNNNYNNYNNNNNNNNNNNNONNNNNNNNNNNYNNNNN	60
247	1	55	0.59	3	.	13	YYNNYNNYNNNYYNNNNNNNYNNNONNNNNNNNNNNNNNN	60
248	0	48	0.59	3	.	6	YYNNNNNNNNNYYYNNNNNNNYNYNONNNNNNNNYNYYNNNNY	60
249	1	51	0.78	3	2.5	23	YYNNNNNNNNNNNNNNNNNNNNNNONNNNNYNNNYNNNN	60
250	0	50	0.66	3	2.9	12	YYYNNNNNNYNYNNNNNNNNNNNNONNNNNNNNNNNNNNNN	60
255	1	54	1.10	1	8.8	12	YYNNNNNNNYNNNNNNNNNYNNNONNNNNNNN NNNNN	260
256	0	55	.	.	.	.	YYNNNNNNNNYNNYNNNNNNNNNNNNONNNNNNNNNNNNYNNNNN	260
257	1	53	0.78	1	2.5	17	YYNNYNYNNNYYNNNNNNNNNYNNONNNNNNNNNNNNYNNNN	60
258	0	48	0.79	2	2.5	10	YYNNYNNYYNNNNNNNNNNNNNNNONNNYYYNNNNYNNNNN	60
261	1	52	0.74	2	5.2	16	YYNNNNNNNYNNNNNNNNNNNNNONNNNNNYNNNNNNNNN	60
262	0	47	.	.	2.5	7	NYNNNNNNNNNYNYNNNNNNYYYYOYNNYNNY	60
263	1	60	0.99	2	2.5	8	YYNNNNNNNYNNNNNNNNNNNNNONNNNNNNNNNNNNNN	60
266	0	47	1.14	10	3.0	48	YYYNNNNNNYNNYNNNYNNNNNNONNNNNNNNNNNNNNNY	60
271	1	66	0.84	4	2.5	15	NYYNNNNYYYNNNNNNNNNNNNNONNNNNNNNNNNNNY	60
272	0	50	0.74	2	2.5	8	YYNNNYNNYNNNNNNNNNNNNNNNONNNYNNNNNNNNNNY	21
273	1	62	0.84	2	4.3	10	NNNNYNNNNYNNNNNYNNNNNNNONNNYNNNNYNNYNNNN	60
274	0	57	0.56	1	3.2	15	NNNNYNNYYYNNYNNNNNNNNNN1NNYNYYNNNNYNNNNNN	60
275	1	54	0.60	1	2.5	15	YYNNNNNNNNYNNNNNNYYNNNNNNNONNNNYNNNNNNNNNN	60
276	0	52	0.99	2	6.2	6	YYNNNYNNNYNYNNYNNNNNNYNNNONYYNNNNNNNNYNNNNN	60
277	1	51	0.70	1	2.5	14	YYNNNNNNYYNYNNNNNNNNNNNNYNONNNNNNNNNNNNNNN	60
278	0	53	0.78	1	2.5	11	NYNNNNNNNNNYYYNNNNNNNNNNNNONNNNNYNNNNNNNNNN	60
281	1	63	0.94	2	2.5	9	YYYNNNNNYNYNYNYYYNNNYNNNONNNYY NNYNNYNNNN	60
282	0	58	0.79	1	2.5	7	YYNNYNNYNNNNNNNNNNNNNYNNNONNNNNNNNNNNNYNNNNN	60
283	1	62	0.99	1	2.5	7	YYNNNYNNYNNYNNNNNNNNNNNNYNONNNNNNNNYNNYNNNN	60
284	0	62	0.84	1	2.5	7	YYNNNNNNNNNYYYNNNNNNNNNNNNONNNNNNYNNNYNNNNN	60
291	1	61	1.21	7	2.5	7	YNNNNYNYYNNYYNNNNNNNNNNNNNONNNNNNNNNNYYNYNN	60
294	0	51	0.89	4	2.5	10	NYNNNNNNYNNYNYNNNYYNYNNNNNONNNYNNYYNNYNNNNN	60
295	1	63	1.01	10	5.1	15	YNNNNNNNNNYNNYNNNNNNNNNNNONNNNNNNNNNNNYNNNN	60
296	0	60	0.84	12	2.5	32	YYYNNNNNNNNNNNNNNNNNNNYNYNONNYNNNNNNYYNNNYN	60
297	1	59	0.70	5	2.5	68	YYYNNNNNNNYYYNNNNNNYYYNNNONNNNNNNNNYNNYNNNN	60
298	0	56	0.70	1	3.2	12	YYNNNNNNNNNYNNNNNNYNNNNNNONNNNNNNNNNNNYNNNNN	60
299	1	64	1.22	5	10.0	13	YYNNNNNNNNYNYNNYYNNNNNNNYYONNNYNNNNNNNNNNNN	60
299	1	57	0.79	1	9.1	19	YYNNNNNNNNYNYNYYNNNNNNNYYONNNYNNNNNNNNNNNN	60
301	1	58	0.79	1	2.5	14	YYNNNNNNNNNNYYNNNNNNNNNNNNONNNNNNNNNNNNNYNN	60
302	0	56	0.94	1	2.5	13	YYNNYNNNNNNNYNNNNNNNNNNNNONNNNNNNNNNNNNNNN	60

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303	1	60	0.79	1	5.9	13	YYNNNNNNNNYNNYNNNNNNNNNNNNONNNNNNNNNNNYNNNN	60
304	0	61	0.99	2	2.5	9	YYNNNNNNYNNYYNNNNNNNNNNNNONNNNNYNNNNNYNNNN	60

EL311	1	55	0.79	3	.	22	YYNNNNNNNNNYNNNNNNNNNNNNYNNNNNNYNNYNNNN
EL312	0	53	0.83	4	.	20	YYNNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNYNNNNNN
EL313	1	64	1.04	5	2.6	25	YYNYYNNYYNYNYNNNYNNNNNNNNONYYNYNNNNNNNNNYN
EL314	0	63	0.64	2	.	12	YYNNNYNYYYNYYNNNNNNNNNNYNONNNNNYNNNYYNNNNNN
EL315	1	52	0.69	1	2.5	27	YYNNNNYNNNNYYNNNNYNNNYNYYONNNNNNNNNNNNYNNNN
EL316	0	50	0.70	2	2.5	7	YYNN NNNNNNYNYNNYYNNNNYYOYNNYNNNNNNNNNNNNY
EL317	1	50	0.70	1	2.5	10	YYNNNNNNNNNYNNNNNYNNYNNNONNNNNNNNNNNNNNNN
EL318	0	50	0.89	1	2.5	6	YYNNNNNNYNYNNYNNNNNNNYNNNNONNNNNNNNNN YNNNNNN
EL319	1	55	0.84	1	7.6	12	YYNNNNNYYYYNNNNNNNNNNNNNNNONNNNNNNNNNNNNNN
EL320	0	53	0.84	2	5.7	22	YYNNNNNNNNYNNYNNNNNNNNNNNNONYNYYNNYNYYNNNNNN
EL321	1	58	0.60	2	3.5	10	YNNYNNNYNNNNNYNNNUNNNNNNNONNNNNNNNNNNNNNNN
EL322	0	56	0.79	2	3.1	13	YNNNNNNNNNNNNNNNNNNNNNNNYNONNNNNNYNNNYYNNNNN
EL323	1	54	0.70	2	4.6	45	YYNNNNNNNNNYNNNNNNNNNNNNNNONNNYNNNNNNNNNNN
EL324	0	54	0.70	1	2.5	14	YYNNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNNNNNN
EL327	1	54	0.59	4	.	15	YNNNNNNNNNNYNYNNNNNNNYNNNONNNNNNNNNNYNNNN
EL328	0	61	0.99	1	.	7	YYYNYNNNNNNNYNNNNNNNNYNNN1NNNYYNNNNNNYNNNN
EL329	1	50	1.04	4	2.5	14	YNNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNYNNNN
EL330	0	48	0.74	1	2.5	3	YYNNNNNNNNNNNNNNNNNNNNNNNONNNYYNNNNNYNNNNY
EL332	0	65	0.91	2	.	6	YYYNYNNNNNNYNNNNNNNNNNNNNONNNNNNNNNNNNNNNN
EL341	1	64	0.88	1	.	20	YNNNNNYYNNNYYNNNNNNNNNNNNONNNNYNNNNNNNNNN
EL343	1	49	0.55	1	.	11	YYNNNYNYYNNNYNNNNNNNNNNNNONNNNNNNYNYNNNNN
EL344	0	53	0.64	2	.	12	YYNNNNNNNNNNYYNNNYNNYNYNONNNNNNNNNNNNNNNNY
EL345	1	53	0.55	1	2.5	58	YYNNNNNYYNYNYNNNNNNNNNNNNONNNNNNNNNNYNNNN
EL346	0	48	0.69	1	2.5	11	YYNNYNNYYNYYYNNNNNNYNNYYOYNNNYNYNNYNNNNN
EL353	1	60	.	.	.	.	YYNNNNNNNNNYYYNNNNNNNNNNONNNNNNYNNNYNNN
EL354	0	62	.	.	.	.	YYNNYNNYNNNNNNNNNNNNNY/NNOYNNNNNNNNNNYNNNNNN
EL357	1	54	0.55	1	.	18	YYNNNNNYYNNYYNNNNNNNNNNNNONNNNNNNNNNYNNNN
EL358	0	57	0.73	1	.	10	YYNNYNNNNYNNNNNNNNNNNNNYNONNNNNNNNNNNNNNNN
EL361	1	69	1.55	1.6	.	14	
EL365	1	69	.	.	.	.	YNNNNNNNNNYNYNNNNNNNNNYNONNNNNNNNNNNNNNN
EM001	1	69	0.92	3	2.5	8	YYNNNNYYNNNNNNNNNNNNNNNNNONNNNNNNNNNNNNNN
EM002	1	55	0.90	3	3.0	300	YYNNYNNNNYNYNNNNNNNNYNNNONNNYNNNNNNYNNYN
EM003	1	63	1.18	4	3.2	44	YYNNYNNYNYNNYNNNNNNNNNNNNONNNYNNNYNNYYNNN
EM004	0	61	0.80	2	3.0	16	YYNNYNNYNNNNNNNNNNNNNYYNNONYNYNNNNNNYNNNNNN
EM005	0	68	1.05	2	2.5	38	YYYNYYYYNNNYYNNNNNNNNYNNONNNYNNNNNNYNNNNNN
EM006	0	62	1.05	3	2.7	53	YYNNYNNNNNYNNNNNNNNNNNNNONNNNNNNNNNNNNNNN
EM007	1	61	0.74	3	2.7	14	NYNNNNYYNNNNNNNNNYNNNNNNONNNYNNNNNNYNNNN
EM008	1	62	1.32	6	2.5	8	YYNNNYNNNNNYYYNNNNNNNYNYNONNNNNNNNNYYNNNN
EM009	0	50	0.92	2	2.5	22	YYNNNNYYYNYYNNNNNNYYYYYYOYNNYYNNNNYYNNNNNN
EM010	0	62	1.30	1	2.5	30	NYNNNNNNNNYNNYNNNNNYNNNONNNNNNNYNNNNNNNNN
EM011	0	51	0.50	2	2.5	4	YYNNYNNNNNYYYNNNNNNNNNYNONNNNNYNNNNYNNNYNN
EM012	0	53	0.51	2	2.5	8	YYNNYNNNNNNNNNNNNNNNYNYN.NNNNNNYNNNYNNNNNY
EM013	0	53	0.62	1	2.5	8	YYNNNNNNNYNNNNNNYNNNNNNONNNYNNYNNNYYNNNNN
EM014	1	67	0.67	1	2.5	23	YYNNYNNNNNYYYNNNNNNNNNYYONNNNNNNNNNNNNNN
EM015	0	53	0.67	1	2.5	16	YYNNNNNYNNNNNNYYNNNNNNNNNONNNNNNNNNYNNNN
EM016	1	65	0.73	2	2.5	11	YYNNYNNYINYNNNNNNNNNNNNNNONNNYNNNNNNNNNN
EM017	1	59	0.92	2	2.5	7	YYNNNNYYNYNNNNNNNYNNYNNNONNNNNNNNNYNNNN
EM018	0	63	0.79	1	2.5	8	NNNNNNYYYNYNYNNNNNNNNNYY1NNNNNNNNNNYNNNNN
EM019	1	62	0.73	1	2.5	38	YYNNNNNNNNNYNYNNNNYYYNNNONNNNNNNNNNYNNNN
EM020	0	70	0.73	3	2.5	10	YYNNNNYYNNNYNNNNNNNNNNNNNONNNNNNNNNNYNNNNN
EM021	0	62	0.92	3	2.5	20	YYNNNNYYNNYNNYNNYNNNNNNNONNNYNNNNNNYYNNNN1
EM022	0	70	0.92	9	2.5	7	YNNNYNNYNNYYYNNNYYYNNYYONNYYNNNNNNYNNNNNN
EM023	0	56	1.05	1	4.5	7	YYNNYNYYNNNNNNNNNNNNNNNNNN1NNNNYNNNNNNNNNNN1

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EM024	0	56	1.19	1	3.4	10	YYNNYNNNNNNYNYNNNNNNNNNNNNONYNYNNNNNNYNNNNNY1
EM025	0	66	1.49	1	2.5	7	YYNNYNYYYNYNYYYNNNNNNYYNNOYNNYNNNNNYNYNNNNNN1

27	0	52	1.09	1	2.5	11	YYNNNNYYNNNYYNNNNNNNNYNNOYYNYYYNNNNYNNNYNN	60
28	0	52	1.00	1	2.5	11	YYNNYNNYNNYYNNNYYNNNNNNN1YYNNYNNNNNNYNNNNN	130
29	0	52	0.87	1	2.5	82	YYNNNYNNNNNYNNNNNNNNNNNONNNNNNNNNNNYYNNNNN	130
30	0	69	0.78	1	2.5	9	NYNNNNNNNNNYYNNNNNNNNNNNONNNNNYNNNNYNNNNNN	130
31	0	50	1.05	12	2.5	7	YYNNNNNNNNYNYYNNNNNNNN/NNONNNNNNNNNNNYNNNNN	130
32	0	56	1.24	15	2.5	15	YYYNYNNYNNNNNNNNNNNNYNNNNONNNYYNNNNNNNNNNN	60
33	0	63	0.91	1	5.7	5	NNNNNNYNNYNNNNNNNNNNNNNN.NNNNNNNNYNNYYNNNN	60
34	1	51	0.67	1	2.5	7	NNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNYNNNNNNN	60
35	0	53	0.67	1	6.3	37	NY NNNYYNYNNYNNNNNNNNNNNNONNNNYNNNNNYNNNNN	0
36	1	63	0.87	1	2.5	22	YYNNNNNNNNYNNYYNNNNNYNNNONNNNNNNNNNYNNYNN	60
37	0	69	1.05	1	5.8	15	YYNYYNNYYNNNNNNNNYNNYNNNONNNNNNNNNNYYNNNNY	21
38	0	66	0.74	1	2.5	5	YYNNNNNYNNYNNNNNNNNNNNYYONNNNNNNNNNNYNNNNN	60
39	0	52	1.09	1	17.1	12	NYNYN NYYYNYNNNYYN NNNNONNNNYNNYNYYNNNNNY	60
40	0	52	0.96	1	2.5	5	NYNNNNYNNNYYNNNNNNNNYNN1/YNYYNNNNNYYNNNNN	60
41	0	60	1.12	1	2.7	6	NYNNNNNYNNYNNNNNNNNNNNNNNONNNNNNNNNYNNNNNN	60
42	1	66	0.86	1	2.5	11	YYNNNNNNNNYNNNNNNNNNNNNNNONNNNYNNNNNYNNNN	60
43	0	55	0.77	1	2.5	6	YYNNNNNYNNNNNNNNNNNNNNNNONNNNNNNNNNYNNNNN	60
44	1	67	1.02	1	2.5	8	YYNNYNNYYNYNNNNNNNNNYNNNONNNNNNNNNYYNNNN	60
45	0	55	0.91	1	3.2	9	YYNNYNNYNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN	21
46	1	52	1.12	1	7.8	17	NNNNNNNNNYNNNNNNNNNNNNYYONNNNNNNNYNNNNNN	60
47	1	67	1.24	4	2.5	43	YYNNNNYYNNYNYNNYYNNNNNNONNNYNNNNNNYNNYN	60
48	1	61	0.97	1	2.5	22	YNNNNNYY NYNNNNNNNNNNNNNNONNNNNNNNNYNNNNN	60
49	0	70	1.07	1	2.5	43	YYYNYNNNNNNNNNNNYNNNNNNNNONNNNNNNNYNYNNNNNN	60
50	1	69	1.12	6	6.5	405	YYNNNNNNNNNYNNYYNNNNNNNNONNNNNNNNYNNYYNNN	60
51	0	54	1.19	5	3.1	24	NYNNNNNNNYYNNNNNNNNNN ONNNNNNNNNNNNNNNNN	60
52	1	50	1.02	1	11.4	12	YYNNYNNNNYYNNN NNNNYYY ONNNNNNNNNYNNNNN	60
54	0	69	0.86	1	2.5	11	NYNNNNYYNNN NNNNNNNNNN ONNNNNNNNNNNYNNNNN	60
55	1	60	0.63	1	2.5	9	YYNNNNNYYNNYNNNNNNNNNN ONNNNNNNNNNNNNNN	60
56	1	62	.	.	.	.	YYYNYNNYNNYYNN NYNNYNN ONNNNNNNNNNNYNNNN	60
57	0	57	0.93	1	7.0	18	NNNN NYYYY NNN NNNNNYY O YNYYNNNYNNN NNNNN	60
58	1	60	0.77	1	4.2	16	NNNNNNNNNNYNYYNNNNNNNNNN ONNNYNNNNNNYNNNN	60
59	1	55	0.92	8	3.2	68	YY N NNYYYYYNN NNNNNNY-ONNNNNYYYNNN NNN	60
60	0	61	0.92	4	4.5	23	YYNNNNYYNYYYYN NNNNNNN ONNNNNNNYNNN NNNNN	130
61	0	62	0.70	3	3.3	11	NYNNNNNYNYYNNN NNNNNYN ONNNYNNNNNNYNNNNNN	130
62	1	63	0.70	3	2.5	22	YYNNYNNYYNYNNN NNNNYYN ONYNNNYNNNNYNNNN	130
63	1	60	0.70	0	3.7	18	YNNNNNYYNYYNNN NNNNNNN ONNNNNNNNYNNNNNNN	.
64	0	60	1.48	37	3.9	46	YYNNNNNNNNNNYYNNNNNNNNNN ONNNYNNNYNYNNNNNNN	130
65	0	59	0.84	3	4.3	11	YNNYNNYNNYYYYNNNNNNNNN ONNYYNNNNNNYNNNNNN	130
66	0	61	1.15	13	8.6	18	YYNNYNNYYYYNYNNNNNNNYN ONNNNNNNYYYYNNNNNN	130
67	0	64	1.04	4	6.1	6	YYNNNYNYYNYYNNNNNYNNNN ONNNNNNNYNYYYNNNNN	130
68	0	57	0.70	0	2.5	6	YYNNYNNNNNNNYNNNNNYYNN ONNNNNNYNNNNNNNNNN	130
69	0	62	0.77	0	2.9	13	NNNNNNYYNN NYN NNNNNNN ONNNNNNNNNNYNNNNNN	130
70	0	63	1.07	3	2.5	9	YYNNNNYYYNNNYN NNNNYNN ONNNNNNNNNNNYNNNNNN	130
71	0	53	0.70	3	4.7	8	YYYNN NYYYYYYYNNNNNNNNY 1NNNNNNNNNNNN NNNNN	1
72	0	67	1.15	21	2.5	10	YYNNNNNYYNNNNNNNNNNNNNN ONNNNNNNNNNNN NNNNN	130
73	0	59	.	.	.	.	YYY YYYYY YN YYNNNNN ONY Y YNNNYN NNNNN	1
74	0	65	.	.	.	.	YYYNYNNYNYYYYN NNNNNNN ONNYYYNNNNNYNNNNN	130
75	1	64	1.31	31	2.6	20	YYNNNNYYNNYYNNNNNNNYYNY ONNNYNNNNNNYNNNN	60
76	1	69	0.77	5	4.6	30	YYNNNNYYNNYNYN NNNNNNN ONNNNNYNNYNYNNNN	60
77	0	66	0.77	4	2.5	18	YNNNYNNYYYYNNN NNNYYYN ONNNNNNNNNYYNNNNNN	60
78	0	66	0.99	3	8.0	11	YYNNYNYYNYYYNN NNNNNYN ONNNNYNNYNYYNNNNNN	0
79	0	55	0.84	0	2.5	8	YYY Y YYNYN NNNNYNN ONNNNYNNNNNN NNNNN	60

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0	59	0.70	3	2.5	7	YNNYNNYYNNNYN NNNNYNY OYYNYNNNNNNNNNNNN	0
0	61	0.92	12	4.0	30	YYNYN YYNYYNNN NYNNNNN ONNNNNNNNYNNYNNN	60

4082	0	57	0.65	1	2.5	22	YYNNYNNNNNYNY	NNNNNN

EM137	1	60	0.82	.	2.5	11	[illegible]	.
EM138	0	60	0.82	1	5.7	16	YYYNNNNNYYYYNYN NNNNYNN ONNNYNNNNNNNYYNNNNN	60
EM139	1	64	0.81	2	2.5	22	NNNNNNNNYNNYNNNNNYNNNNNNNNNONNNNNNNNNNNNNNN	60
EM140	0	62	0.77	3	2.5	15	YYNNYNNYNNNYNN NNNNNNNNNONNNNNNNNNNNN NNNNN	60
EM141	0	60	0.53	1	2.5	13	YYNNNNNYYNNNNYYNNYNNNNNNONNNNYNNYNNYNNNNNN	60
EM142	1	58	1.14	1	2.5	11	NYNNNNNNNNYNNYNNNNNNYNNNONNNNNNNNYNYNNNNN	60
EM143	0	53	0.77	1	2.5	10	YYNNYNNNNNNNYNNNNNNNNNYNONNNNNNNNNNNNNNNNN	60
EM144	0	50	0.57	1	7.2	11	YYYNNNNNYNYNYYYNNNNNNYNNONNNNYNNNNNNYNNNNN	60
EM145	0	37	0.57	1	2.5	16	YYNNNNNYNNNNNNNNYNNNNNNNNONNNNNNNNNNYNNNNNY	60
EM146	0	60	0.99	1	2.5	20	NYNNYNNNNYNNNYNNNNNNYNYYONNNNNY NNNYNNNNN	60
EM148	0	52	1.19	7	11.8	21	YYNNNNNNNNYNYYYNNNNNNNYYOYNNNYNNNNNNYNNNNY	60
EM149	0	68	1.94	26	3.1	11	YYNNYNNYNYNNYNNNNNNNNNNNNONNNNNNNNNNYNNNNNN	60
EM150	1	58	0.90	1	5.1	20	YYNNNNNYNNYNYNNNNNNNNNNNNONNNNNNNNNNNNNNNN	60
EM202	0	66	0.78	3	11.3	37	NNNNNNNNYYYNNNNNNNNNNNNNNNONNNNNNNNYNNYNNNNN	60
EM207	1	66	1.00	1	2.5	23	YYNNNNNNYYN NYNNNNNNNNNYNONNNYYNNNNNNNNNNN	60
EM210	0	.	0.85	1	2.5	11	.	.
EM211	1	64	1.05	8	2.5	21	YYNNNNNNNNNYNNNNNNNNNNNNNONNNNNNNNNNNYNNNN	60
EM212	0	60	0.84	1	3.7	8	YYNNNYNNYNN NNNNNNNNNNNNNONNNNNNNNNNNYNNNNN	60
EM214	0	63	1.25	1	2.5	38	Y NNNNNNYNYNNNNNNNNNNYNNNONNNNNNNNNYNNNNNNN	60
EM217	1	.	0.78	1	5.9	14	.	.
EM219	1	62	1.00	5	4.8	8	NNNNNNNNNNYNNNNNNNNNNYNNNONNNNYNNNYNNYNNNN	60
EM220	0	52	.	.	.	.	NYNNNNNNNNYNNNNNNYNNNNNNNONNNNNNNNNNNYNNNNNN	60
EM221	1	66	0.78	5	2.5	20	YYNYNNNYNYNNNNNNNNYNNNNNYNONNNNNNNNNNNYNNN	60
EM222	0	57	0.93	3	2.5	6	YYNNNYNNNNYNNNYNNNNNNNNNNNONNNNNNNNNNNNNNNN	60
EM223	1	64	1.22	5	8.3	18	NNNNNNNNNNYNNNNNNNNNNNNNNNONNNNNNNNNYNNYNNNN	260
EM224	0	63	.	.	.	.	NYNNNNNNNNYNNYNNNNNNNNNNNNONNNNNNNNNNNYNNNNNN	260
EM225	1	61	0.76	2	2.6	13	YYNNNNNNYNNYNNNNNNNNNNYNNONNNNNNNNNNNNYNNNN	60
EM226	0	58	1.11	2	2.5	11	YNNYNYYYNNNNNNNNNNNNNYNOYNNNNNNNNNNNYNNNNN	60
EM227	1	60	0.63	5	3.4	21	Y NNNNNYYNYYNNNNNYYYNYYONNNN NNYNYNNNNNN	60
EM228	0	50	0.70	5	2.5	8	YYNNNYNNNNNYNNNNNNNNNNYNONNNNNNNNNNNYNNNNNN	60
EM229	0	60	0.90	1	6.0	16	Y NNYYNYNYNYNNNNNNN NNYOYNNYYNN	60
EM233	1	57	1.16	6	4.7	16	YYNNYNNNNYNNNNNNNNNNNYNNNONNNNYNNNNNNNNNN	60
EM234	0	59	1.08	7	3.5	26	NYNNYNNNNYNYYNNNNNNNYYNNONNNNNNNNYNNYNNNNN	60
EM235	1	37	0.85	3	3.0	11	NYNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNYNNNN	60
EM236	0	58	0.78	5	2.5	5	YYNNNNNNNNNNNYNNNNNNNNNNNONNNNNNNNNNNYNNNNN	60
EM239	1	59	1.00	3	.	11	YYNNNNNNNNNYYNNNNNNNNNYNONNNYNNNNNNNNNNN	60
EM240	0	61	1.00	2	.	18	YYNNYNNNNNNYNNNNNNNNNNYNNNONNNYNNYNNYYYNNNNY	60
EM241	1	58	0.79	1	3.3	20	YYNNNNNNNNNYNYNNNNNNNYNNNONNNNNNNNNNNNNNNN	60
EM243	1	57	0.63	5	.	28	YYYNNNNNY NYNNNNNNNNYYYNN1NNNNYYNNNNNYYNNY	60
EM244	0	59	1.08	5	.	16	YYYNNNNNNYNNNNNNNNNNNNNONNN NNNNNNNNNNNNN	60
EM245	1	53	1.16	4	.	20	YYNNYNNNNNYNYNNNNNNYYNYYONNNNNNNNNNNNNNN	60
EM246	0	53	.	.	.	.	YYNNNNNNNNYNNYNNNNNNNNNNNONNNYNNNYNNYNNNNN	60
EM247	1	52	0.94	1	2.5	30	YYNNNYNNNNNYNYNNNNNNNNNNNONNNNNNNNNNYNNNN	60
EM248	0	52	0.65	1	2.5	8	YYNNYNNNNNNYYNNNNNNNYNNNONNNNNNNNNNNYYNNNNN	60
EM251	1	57	1.08	7	.	12	YYNNNNNNNNYNNYNNNNNNNNNNNONNNNNNNNNYNNYNNNN	60
EM252	0	53	0.93	3	.	7	YYNNNNNNNNYNNNNNNNNNNNNNNOYNNNNNNNYNNYYNNYNN	60
EM254	0	55	0.83	4	3.6	10	.	.
EM257	1	52	.	.	.	.	YNNNNNNNNNNNNNNNNNNNNNNNONNNNNYNNNNYNNNN	60
EM258	0	50	0.93	4	.	12	YYNNNNNNNNNYNNNNNNNNNNNNONNNNYNNNNNNNNNNN	60
EM260	0	67	0.93	4	.	9	YYNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNYNNNNN	60
EM261	1	50	0.74	1	2.5	13	YYNNNNNNNNYNNYNNNNNNNNNNNONNNNNNNNNNNNNNNN	60
EM262	0	45	0.79	1	2.6	8	YYNNNNNNNNN YYNNNNNNNNNYNONNNYNNNNNNNNN NY	60
EM263	1	66	1.08	3	.	23	YYNNNNNNNNYNYYNNNNNNNNNNNNONNNNNNNNNNYNNNN	60

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EM264	0	66	0.93	5	.	14	Y NNNNNNNYNNNNNNNNNNYNNNONNNNNNNNNNNNNNNN	.
EM266	0	62	1.05	1	10.4	11	NYYNYNNY YNNNNNNNYNNNNNNONNYNYNNNNNNNNNNN	60

EM268	0	61	0.94	1	3.4	17	NYSPSTPNTTYNNN

E0004	1	54	0.92	3	2.5	16	YYNNYYNNNNNYYNYNNNNNYNYNNNNN

EP172	0	52	0.72	2	.	7	YYNNNYNNNNYYYNNNNNNNNNNNONNNNNNNNNNNYNNNN	26
EP173	1	53	1.09	6	2.5	12	YYNNNYNNNNYYYNNNNNNNNNNNONNNNNNNNNNNYNNNN	26
EP176	0	52	0.77	1	2.5	10	N NNNNNNNNNNNYNNNNNNNNNNNONNNNNNNNNNNNNNY	26
EP177	1	52	1.03	1	2.5	72	YYNNNNNNNNNNNNNNNNNNNNNNOYNYY YYNNNYNNNN	6
EP178	0	49	0.68	1	2.7	11	YYNNNNNNNNNNYNNNNNNYYNNNONNNNNNNNNNNYNNNNY	6
EP179	1	60	.	.	.	.	YNNNNNNNNNNYNNNNNNNNNYNNNONNNYNNNNNNNYNNNN	6
EP180	0	59	0.82	1	4.4	8	YYNNYNNYYNYNNNNNNYNNNNYNONNNNNNNYNNNYNNNNNN	6
EP181	1	54	0.51	2	.	10	YYNNYNNNNNYNNNNYYNNNNNNONNNNNNNNNNNNNNNN	26
EP182	0	52	0.66	2	.	6	YYNNNNNNNYNNNNNNNNNNNNNNONNNNNNNNNNNNNNY	26
EP183	1	51	0.72	1	2.7	20	*	
EP184	0	49	0.82	1	2.5	11	YYNNNNNNNNNNYNNNNNNNNNNNONNNNNNNNNNNYNNNNY	26
EP185	1	50	0.86	5	.	15	NYNNNNNNNNYNNNNNNNNNNNNNONNNNNNNNNNNNNNN	26
EP185	1	50	0.86	5	.	15	YNNNNNNNNNYNNNNNNNNNNNNNONNNNNNNNYNNNNNNN	26
EP189	1	60	0.68	1	2.5	9	NYNNYNNNNNYYNNNYNNNNNNNNONNNYNNNNNNNYYNNN	26
EP192	0	56	0.82	7	2.5	6	YYNNYNNYNNNNNNNNNNNNNNNONNNYNNNNNNNNNNNNN	6
EP193	1	55	0.72	3	.	17	YYNNNNNNNNYNNNNNNNNNNYYONNNNNNNNNNYYNYNN	26
EP194	0	52	0.55	2	.	6	YYNNYNNNNNYNNNNNNNNNNNNONNNYNNNNNNYYNNNNN	26
EP195	1	53	0.77	1	2.5	26	YYNNNNNNNNNYYNNNNNNNNNNNONNNNNNNNNNNYNNNN	26
EP196	0	49	0.82	1	2.5	11	YNNYNNNNNNNYNNNNYNNNNNNONNNNYNNYNNYNNNNNN	26
EP201	1	64	0.82	1	3.7	540	NNNNNNNNNNYNYNNNNNNNNNNNNONNNYNNNNNNNYNNNN	26
EP202	0	60	1.03	1	2.5	28	YYYNNNNYNNNNYNNNNNNNYNNNONNNYNNNNNNNYNNNNN	26
EP207	1	66	.	.	.	.	YYNNNNNYNNYNNNNNNNNNNNNNONNNNNNNNNNNYYYYN	6
EP217	1	63	1.05	2	.	11	YYNNNNNYYYYNNNNNNNNNNNNNNONNNNNNNNNNYNNNN	13
EP218	0	53	0.77	2	.	9	YYNNNNNNNNNNYNNNNNNNYNNNONNNNNNNNNNNYNYNNN	6
EP223	1	60	0.88	4	.	15	YYNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNNNNN	13
EP224	0	58	.	.	.	.	YYNNNNNNNNNNNYNNNNNNNNNNNONNNNNNNNNNNYNNNNN	6
EP225	1	62	0.66	2	.	15	YYNNYNNYNNYYNNNNNNNNNNNNNONNNNNNNYNNYNNNN	26
EP227	1	56	1.05	5	.	46	YYNNNNNNNNNYYYNNNNNNNNNNNONNNNNNNNNNNNNNN	26
EP229	1	60	0.86	2	.	11	NYNNNNNNNNNYNNNNNNNNNYNNNONNNNNNNNNNNNNNN	13
EP232	0	66	0.66	2	.	9	YYNNYNNYYN YNNNNNNYYYYYOYNNNNNNNYNYYYYNNY	6
EP260	0	.	1.25	4	4.3	11		
ES001	0	52	0.51	3	2.5	8	YYYNYNNN NYYYN NNNNNNN 1NNNNYNYNNNN NNNNN	6
ES002	1	60	1.04	10	2.5	16	YYNNNNNN NYNNN NNNNNNN ONNNNNNNNNNNNNNN	6
ES003	1	65	0.79	3	4.7	24	YYYNNNNY NYNNN NNNNNNN ONNNYNNNNNNN NNN	6
ES004	0	52	0.62	5	2.5	6	YNNNYNNYYY YNN NNNNYNN ONNNNNNNYYYYNNNNNN	6
ES005	1	56	0.92	2	3.4	8	NYYNNNYYNY NNN NNNNNNN ONNNNNNNYNNYNNNN	6
ES006	0	66	0.79	2	2.5	7	YYNNYNYY NNYNN NNYYYNN ONNNYNNNNYNYNNNNNN	
ES007	1	70	0.73	1	2.5	14	YYNYNNYYNNYNYYYYNNNNNN 1NYNNYNNNNNYYNNN	
ES008	1	53	0.83	12	2.5	44	YYYNYNYYNNYNNYNYNNNNNN ONNYNNYNNNNN NNN	
ES009	0	51	1.42	6	2.5	33	YYNNNYNYYNY NNN YNN YYY OYYNYYYNNNYN YNNNY	6
ES010	1	56	1.14	9	2.5	13	YYYN NYYNNYYYN NNNNNYY ONNNNNNNNNYYNNNN	6
ES011	0	62	0.96	1	3.0	8	YYNNNNNYNNNYNYY NNN YY 1NYYYYNNNN YYNNYNY1	6
ES012	0	53	1.09	1	2.5	5	YY NNNYYNNNNYYYYNNYYY N 1NYY YNYYNYYYNNYNY1	6
ES013	0	69	1.19	1	5.9	55	YYNNYNNYNNYNYN NNNYYYY ON NYYYYYNYYNNNNNN	6
ES014	0	56	0.63	1	2.6	11	YYNNYNNYNNNYNN NNNNYNY 1NNNNNYN	1
ES015	0	59	0.87	1	6.3	13	YYNNNNNYNY YNN NNNNNYN ONNNYNNNNNNN NNYNN	6
ES016	1	55	0.96	1	3.7	11	NNNNNNYN NNNNN YNNNNNN ,NNNNNNNNNNYNNNN	6
ES017	0	51	0.96	1	3.4	25	YYYNNNNYNY NNN YNNNNNY OYNNYNNNYNYYNNNNNN	6
ES018	1	67	0.87	1	4.0	28	YYNNNYYY Y NNN NNNYYYN OYNYYNYYYYYNNNNN	6
ES019	0	62	1.05	1	3.7	7	YYNNYNNY NYNYN YYNNYNN ONNNNYNNNNNYNYN NN1	6
ES020	0	56	1.19	1	4.8	14	NYNNNNNYNY NYN NNNNNNN ONNNNNNNNNNYNNNNNN	6
ES021	1	56	1.09	1	2.6	26	YYNNYNNYNY NYN NNNNNNN ONNNYNNNNNNYNNNN	6
ES022	1	60	0.78	1	6.8	11	YYNNYNNN Y NYYNNNN YYY OYNNYYNNYNYYYNNN	6

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ES023	1	61	1.05	12	2.8	15	YYNYNNY NYNYYYNYNNYNN ONNNNYNNNNNYNNNN	6
ES024	0	68	1.09	1	3.6	14	YYNNYNNY Y NNNNNYNNYNN ONNNNYYNNNYYYNNNNN	6

ES025	1	54	1.00	1	3.6	52	YYYNNNYY NYYYN NNNNNNN ONNNNYNNNNNYNNNN
ES026	1	61	0.98	20	3.1	37	YYNNNNNN Y NNN NNN NNN ONNNNNNNNNNNYNNNN
ES027	1	57	0.87	1	3.0	31	YYYNNNNYYNYNNN NNNNNYY OYYYYNNYNNNN NNN
ES028	0	55	0.82	1	2.5	20	YYNNNNNN NYYYN NYNNNYN ONNNYNNNNNNYYNNNNNN
ES029	0	50	0.93	1	10.1	7	YYYNYNNY Y YYN YYNNNYNY ONNNYNNNYNYN NNNNY
ES030	1	69	0.77	1	3.4	8	Y NNYNNYNY NNN N NNNNN ONYNNNYNYNNYN NN
ES031	1	55	0.87	1	5.3	10	YYYNYNNYNNYNNYYNNNNNNN ONNNYNNNNNYYNNNN
ES032	0	47	1.44	1	7.5	7	YYNYN YYNY YNY YYNNNYN ONNNNNNNYNNYYNNNNY
ES033	1	52	1.08	1	6.1	19	YYNN NNN Y NNN YYNNNNN ONNNNNNNNNNN NNY
ES034	0	53	0.77	1	2.5	16	YNNNNNYY NNNNN NNNNNNN ONNNNNNNNNNYN NNNY
ES035	0	51	0.87	1	2.5	7	Y N NNYNNN NNNNYNN ONNNNNNNNNNNYYNNNNN
ES036	1	66	0.77	1	3.1	8	YYNNYNNY Y YNN NNNNNNN ONNYNNNNNNNNYNNNN
ES037	1	68	0.77	3	2.9	14	NYNNNYNYNNNNNNN NNNNNNN ONNNNNNNNYNNN NNN 1
ES038	0	60	1.15	5	4.7	9	YNYNYNNYNY NNN NNNNNNN ONNNNNNNNYNYYNNNNNN1
ES039	0	53	0.92	3	3.1	10	YYNY N YNNYYNYYNY N NN ONNNYNNYYNNYNYNYNN
ES040	1	63	0.84	2	3.4	8	YYNNNNNN NYNNN NNNNNNN ONNNYNNNNNNNYNNNN 1
ES041	0	60	0.89	2	3.2	22	YYNNYNYYNNNNNYN YNNNYNN ONNNNNNNNNNYYNNNN 1
ES042	0	50	0.84	1	6.7	14	YNNNNYNNNNYNYNNNNNNNNN ONNNNNNNNNNNYNNNNN1
ES043	0	51	0.92	3	3.6	33	YNNNNNN NNNNN NNNNYNN ONNNNNNNNNNYNNNNY
ES044	0	57	0.77	3	2.5	11	YYNNYNNY NYYNN NNNNNYY ONY YNNNYNNYYNNNNN
ES048	0	57	.	.	.	.	YYYNNNNYYNNNNNNNYYNNYNN OYYYYNNNNNNYYNNNNN1
ES049	1	53	0.87	1	2.5	19	YYNNYNNN NYNNN NNNY NN ONNNNNNNNNNNYNNNN 1
ES050	0	50	0.70	1	2.6	7	YYNNNYNYNY NNN NYNNNNY ONNNNNYYYYNN NNNY 1
ES051	0	50	0.80	4	2.5	32	YYNNYNNN YYNYN NNNNNNYYONNNYYNNNNNNYNNNNN1
ES053	0	67	0.90	7	3.0	18	NNNNYNNNNNNNNYN NNNNNNN ONNNNNNNNNNYNNNNN 1
ES054	0	70	0.70	4	3.1	10	YYNNNNNN YYNNN NNNNNNN ONNNNNNNYNNYNNNNN1
ES055	0	57	1.40	11	6.6	18	YYNNYNNYNYYNNYNYNNNYNN 1NNNNYNNNNNN NNNNY
ES056	1	69	0.80	2	9.3	13	YYNNYNNYNNYNN NNNNYNN ONNNNNNNNYYNYYNNN 1
ES057	0	59	0.80	2	10.4	16	NNNNYNNYYYYNNN NNNNNNN ONNNNYYNYNNN NNNNN
ES058	0	55	0.69	6	2.5	22	YYNYYNNYYNNNYN NYNNNNY ONNNNYYNNNYYYNNNN2
ES059	1	66	0.62	1	2.5	12	YYNNNNNNNNNNNYN NNNNNN ONYYNNNNNNNNYNNNN 2
ES060	1	70	0.68	3	2.5	13	NNNNYNYYNNYYYN NNNNNNN ONNNYNNNNNNYNNNN 2
ES061	1	55	0.64	6	2.5	23	YYNNYNNNNNYNNNNNNNNNNNNNONNNYNNNNNNYNNNN 2
ES062	0	62	0.94	4	5.1	13	YYNNNNYYNNYNNNNNNNNNN .NNNNNNNN YYNNNNNN2
ES063	1	58	0.76	2	2.5	47	YYYNNNNYNYNYYN NNNNNNN ONNNYNNNNNNN NYN 2
ES064	1	55	0.94	1	13.7	46	YYNNNNNN YYNNNNNNNNNNNN ONNNYNNNNNNYNNNN 2
ES065	0	55	1.30	12	8.3	23	YYNNNYNYNYYNYN NNNNNYYNONNNYNYNYNYYNNNYN2
ES066	0	61	1.07	0	3.9	20	YYNYNNNYNYNNNN YYNNNNNNONNNNNNNNNNNNNN N2
ES067	1	51	0.91	5	16.3	37	YYNNYNNYNYYNNN NNNNNNY ONNNNNNNNNYYYNYY 2
ES068	1	61	1.13	9	4.0	17	YYYNYNNYNYYNYN N NNNNN ONNNNNNNYNYN NNN 2
ES069	0	53	1.05	0	5.1	14	YNNNYYNYNYYNNN NNNNNNN ONNNYNNNYNNN NNNN2
ET001	1	82	1.77	8	3.6	9	YYNNNNNYYNYNNY YNNNNNN OYYYYYNYNNNNNNNN
ET002	1	73	0.98	3	5.7	9	YYNNNNNY NYNNYYYNNNYNNYOYYYYNNNNNYNNYYN
ET003	0	78	1.11	3	4.7	13	YYNNYNNNNNYYNYYYNNNNNYYOYYYYNNYNNNYYNNNN
ET004	1	77	0.98	5	25.0	35	YYYNNNNYNY YNYYYNNNNNY ONYNNYNNYNYYNNNN
ET005	0	80	2.18	29	4.1	9	YYNNYNNYNNNYNYYYNNYNYYYONNNYNNNNNNNYNNNNN
ET006	1	57	2.18	87	2.8	27	YNNNNNNNNNNNYYYYNNNNNY ONNNNNNYNYYNNNN
ET007	0	55	3.40	134	250.0	44	Y YN YNYYNNNNYYYY YYYY 1YNYNYNNNNNY NNNNY
ET007	0	55	3.40	134	250.0	44	YNNNNNNNNYNNNNNYNNNNNYYYOYYNNNYYYNNYYNNN
ET008	1	56	1.32	4	9.9	10	YNNNNNNNNNNNYNNNNNNNNNNON YNYYNNNNYNNNN
ET009	0	68	2.70	98	6.8	22	NNNNNNNNNN NYYYNYY YN .N N NNNNNNNNNYNN
ET010	0	54	1.59	17	237.0	17	YYNNNNNNNNYNNNYYYNNNNNN ONNNNNNNYYYYNNNNNN
ET011	0	68	1.02	2	9.1	15	YY YYYYY YYY YY YY 0 YYYY YYY Y

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ET012	1	78	1.80	76	168.0	16	YYYNNN YYNYNNYYYNNYYYN .Y NYYNNNYNYNNNNN
ET013	1	67	1.82	15	250.0	27	NYNNNNNNNNYNNNYYYNNNNNN ONNNNYNNNNNYNNNN

014	0	69	1.99	3	35.4	5	YYNNNN NNYYNYYYNNNNNNNY 1NYYNNNNNNNYYNNNNN
015	1	70	1.82	26	14.9	19	YNNNNNYYYYNNYYYNYYNNN OYNNNNNNNYNNYNNNN
016	1	50	0.82	2	4.1	11	YYNNNNNNNNNYNYN YNNNNNN ONYNNNYNNN YNNNN
017	0	82	1.02	9	42.0	6	YYYNYNNY NN NYYNYNYYYYNOYYYYYYYYNNNYYYNNNN
018	0	83	0.76	2	3.8	7	YY Y YYNN N N NNNN NN ONN NN NNYNNNN
019	0	53	3.10	86	4.0	13	YYYNNN YYYNNNYYYNNNNNY ONNNNNNNNNNNYYNNNNN
020	0	83	1.51	19	6.7	12	YY Y YYNNYYYYYNNYYYY ONNNNYYNNNYYYNNYNN
021	0	71	0.59	3	6.3	13	.
022	.	.	.	.	.	.	YYNNNNNYYY NNYNYNNNNNYYONYNNYNNNNN NNY
023	1	67	0.82	2	55.6	92	YYNNYNNYYNYNNN NNYYYNN ONNNNNNNNN YNNNY
024	0	83	0.70	1	4.9	17	YNNNNN NNNNN NNNNN ONN NNNNNNNNNNNNN
025	0	85	1.51	12	5.6	6	NNNN NNYYNNNNYYYNNNNNN 1NYNYNNNNNNYYNNNNN
026	0	79	0.82	1	7.2	160	YYYNNNYYNNNNNNNNNNNNYNNN1YYNNNYNNNNYNNNNNN
027	0	77	0.48	1	7.6	20	YYNNYNNNNNNNNNYYNNNNNNNNNOYNYNNYYNNNYNNNNN
028	0	70	1.44	11	40.8	7	YNNNNN YNNNNYYYN YY N1NYYYYNNYNYN NNYNN
029	1	66	1.82	95	250.0	165	.
030	1	62	2.27	78	21.6	19	YYNN NNNNNN NYYYNNYNN YONNNYNNNNNNYNNNY
031	0	77	2.71	108	10.9	50	NYNNNNNNNNNYYYYYYYNNYYNNONNNNNNNNYNNYNNNNNN
032	0	71	1.24	6	234.0	42	YYNNNN YYNYY YNNNN . YY NY NN NN
033	1	66	2.54	105	19.7	48	YYYYYYYYYYYNYYNNYNY YYY OYYYYYN YYYYYYYY
034	0	80	0.83	10	6.5	19	YYNNNNNNYYNYNNN NNNNN N . YNNYYNNNNN NNNNN
035	1	69	1.42	14	36.0	57	YYNNYNNNNNY NNNNNNNNN 1NNNNNNNNNNYYNNN
036	0	69	1.83	17	9.6	14	YNYNNNYYNYNNNNYYYNNNNYYYONNYYNNNNNNNNNNNN
037	1	85	1.55	12	24.2	12	YYNNYNNYNY NYN YNYYYYN 1NNYNYNNNNNYNNNN
038	1	54	2.18	26	17.4	10	YYYNNNNYYYYYNYYYYYYYNNY .NYYYYNNNNYNNNNN
039	0	.	.	.	.	.	YYYNNNNNYNYYNNNNNNN YYYONYY YNYNNYYNNNY
040	0	58	0.81	1	3.0	9	YYNNYNNYYNYNNYYNNNNYNN ONNYNYNNNNNNYNNNYNN
041	1	65	1.30	21	27.2	17	YYNNNNNNNN YNNN NNNNNNN ONY NYNNNNNYNNNN
042	0	.	.	.	.	.	NNNNNNNNNNYYNNYYYNNYYYY 1NNYNNYYYNYNNNNN
043	1	.	0.74	1	14.2	8	.
044	0	71	0.89	1	11.1	7	NNNNNNNN NNNYYYYNYYYYN ON NNNNNNNNNN
045	0	76	0.94	4	6.3	6	YYNNYNNYNNYNYYYYNNNNNY 1YYYNYYYNNYYNNNNNN
047	0	66	1.30	3	4.3	12	NYNNNNNN NNNYYNNNNNNNY 1YYNYNNNNNYYNNYNN
048	1	62	1.68	13	2.5	16	YYNNYNNNNNYNNN YNNNNNY 1NYYYNYYNNNYYNNN
049	1	77	2.87	42	12.8	8	YYYNNNNNNNYNNNNNYNNNNNNNNOYNYNYYYYNNYYNNN
050	1	75	1.44	11	12.8	9	YYNNNNNYNYNNNYYYNNNNNNNNOYYNNNYNYNNYYNNN
052	0	65	1.88	13	10.7	12	YYNNNNNYNYNYNYYYNNNNYY 1YYYNNNNYNNYYNNNNN
053	1	81	1.04	4	2.9	8	YYNNYNN YNYNNNNNNNNNNN .NYNNYNNNNNYYNNN
054	1	61	1.50	32	5.6	53	YYNNYNNNNYNNNYYYNNYNYYYONNNNYNNNNNYNNNN
055	1	81	1.15	27	7.8	17	NNNNNNN YYNNNNYNNNNNY OYYYNYNYYNNYYNNN
055	1	81	1.15	27	7.8	17	NNNNNNNYNYNNNYYYNNNNNNNNONYYNNYNYNNYNNNN
056	1	70	.	.	.	.	YYNNNNNYNNNNNN NNNNN . YY YNYNNN NNN
057	0	.	1.50	40	10.0	22	.
058	1	71	1.31	4	8.0	9	YYYNNNNNNNNYNNN NNNNNNN 1YYYYNNNNNNNYYNNN
059	1	80	1.31	8	15.3	6	YYNNNNNNNNYYNNN YNNNNNY 1NYYYNNYNNNYNNNN
060	1	.	2.43	98	16.4	47	.
061	0	71	0.99	5	4.0	16	YYYNYNYYNNYYYN YYNNYNY 1YYYYNYNNNYYNNNNNN
062	0	.	1.10	6	46.0	400	.
063	0	.	0.76	11	24.5	330	.
064	0	54	1.04	8	3.6	3	YYNNYNNYNNYNYN NNNNNYY 1YYYY YYNNNNNNNNNN
065	1	74	0.68	1	7.1	13	YYYNNNNN Y NNN YNNNNYYY1NYNYNNNYNNYYYNN
066	1	72	1.06	4	3.6	11	YYNNYNNYNYNN YYYNNNNNNNNONNNYNNNNNNYYNNN
067	1	59	1.99	11	2.7	15	NNNYYNNNNNNYNYYY YNNNNYY1NN NYNNNNNYNNNN

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068	1	60	1.61	8	7.3	16	YNNNNNNN NNNYN NNNNNYNN1YNNYYYYNNNNNNNNNN
069	0	60	1.40	18	42.4	10	YYNNNNNYYNYYYYYYNNNNYYYONYNNYNNNNNNYYNNNN

ET071	0	60	2.00	37	161.7	38	YNNNNNNNN NNNYNNNNNNNNNYNNLYNNYYYYNNNNNNNNNN
ET072	0	71	1.87	28	91.1	9	YYNYNNNYYYNYYNYYYNNNNNNNNONNNNYNNNNNNYNNNNNN
ET073	0	57	1.39	45	9.1	31	YYYNYNNYNYYYYYYYNNNNYYYOYYNNYYYYYNNNNNNNNN
ET074	1	66	1.20	19	3.8	9	YYNNNNNNYYYYNYYYYNNNNYNNONYNNYNNNNNNYNYNY
ET075	1	72	0.85	0	3.9	52	YYYNNNNNYYNYNYYYYNNYYYYYONYYYNNNNNNNYNNNN
ET077	1	69	2.09	23	5.2	61	YYNNNYNNNNYNNNYYYNNNYNYYONNYYNNNYNNYYNNN
ET078	1	52	1.18	7	250.0	7	YYNNNNNNYNNNNNYYYNYYYYNNONNNNNNNNYNYYNNNN
ET079	0	62	1.23	20	2.5	7	YYNNNNNN NNNYN YNNYYNNYONYNNNNNYNYYNNNNNN
ET080	0	76	1.50	19	9.1	15	YYNNYNNNNNYNYNYYYNNNNYYYONNNNYNNNNNYYNNNNN
ET081	1	74	1.61	53	4.1	34	YYNNNNNYNYNYNYYYNNNNYYYONYYNYYNNNNNNYNN
ET082	0	76	2.00	49	54.5	16	NNYNNNNNNNNNNYYYYNNNYYNN.NNNNNNNNNNNNNNNNN
ET083	0	80	2.21	73	5.3	17	YYYNNNNNNNNYNNYYYNNN YYYOYYYYNNYNNNYNNNN
ET084	1	53	0.76	1	5.6	18	YYNNNNNNNNNYNYNNNNNNNNNNNONNYY YYNNNNNNNN
ET085	1	80	1.94	23	7.6	34	YYNNNNNNYNNYNNYYYNYYYYNNONNNNNNNNNNNYYNNN
ET086	0	74	2.31	35	5.0	11	NNNNNNNNNNYNNNYYYNNNNNYYONNYNNNNNNNNYNNNNNN
ET087	0	48	1.50	23	12.0	.	NNNNNNNNNNNNNNNYYNNNYYYNNONNNNNNNNNNNNNNNYN
ET088	1	62	1.04	4	10.3	31	YNNNNNNNNNYNNNYYYNNNNYYYONNNNYNNNNNNYNNNN
ET089	0	58	1.11	3	8.6	14	NNNNNNNYNNYNNNYYNNNNNYYYONYYYNYNNNNNNNNNNN
ET090	1	63	1.04	5	3.1	16	YYNNNNYY NYNNNNYNNNNNYYOYYYNYYYNNNNNNNN
ET091	1	68	0.96	3	14.2	12	NNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNYNNNNN
ET092	1	66	2.07	13	50.0	26	YNNNNNNNNNNNNNYYYNNNNYYYONYYYNNNNNNNYNNNN
ET093	0	61	0.72	1	2.5	21	NNNNNNNNNNNNNNYYYNNNNNYYONYYYNNNNNNNYNNNNNN
ET094	0	66	1.29	13	250.0	94	NNNNNNNNYNYNNNYYYNNNNNNNOYYYNYYNNNNNNNNNNN
ET095	1	74	1.82	16	173.0	16	YYNNNYNNYNYNNNYYYNNNYNNN1YYYNNYYNNNYYNNN
ET096	1	74	1.16	23	250.0	350	YYNNYNNYNYNNYYYYNNNNNYYOYYYNNYNNNNYYNNN
ET097	1	60	1.39	3	97.5	22	YNNNYNNNNNYNNNYYYNNNYNYY1NYNNYNNNNNNNNN
ET098	1	72	0.93	3	12.8	15	YYNNNNYYNYNNNYYYNNNYNYYONYNYNNNNNNNYNNNN
ET099	1	66	1.22	17	74.0	8	YYNNNNNNYNYNNNYYNNNNNNNNNONNNYNNNNNNNYNNNN
ET100	0	68	1.46	2	13.6	5	YYNNNNNNNNNNNNYYYNNYNYYNONNNYNNNNNNNNNNNNN
ET101	1	73	0.83	3	.	11	YYNNNNYYNNNNNYYYNNNNNNNNOYYYNNYYYNNYNNNN
ET102	1	68	1.34	8	.	30	YYNNNYNNNNYNNNNNNNNNNNN1YYYYNYYYNYNNNNN
ET103	1	70	0.83	4	.	14	YYNNNNNNNNNNNNYNNNNNNNNNNN1YYYNNYYNNNYNNNN
ET104	1	62	2.27	78	21.6	19	. NNNNNNNNNNYNNNYYYNNNYYY ONNNNYNNNNNYYNNN
ET105	0	62	1.01	2	13.7	5	NNNNYNNYNNNNNNNNNNNNNNNNNOYNNNNYYNNNNNNNNNN
ET106	0	53	3.20	403	107.4	170	YNNNNNNNXNNNNYYYNNNNNYY1YYYYNYYNNYNNYNNNNN
ET107	1	.	0.76	1	2.5	30	YYYNNNNYYNNNNYYYYYYYYYYNONNNYNNNNYYNNNNNXX
EV001	1	56	0.74	1	2.5	19	YYYNNNNN NYNYN NNNNYNN ONNNYNYNNNYYNNYN
EV002	0	51	0.74	1	2.5	7	YYNNYNNYYNNNYN NNNNNNN ONNNNNNNNNNNYNNNNNN
EV003	0	49	0.78	1	2.5	6	YYNNNYNNNNNYYNNNNNNNNNNNONNNYNNNNNNNYNNNYN
EV004	0	64	0.59	1	2.5	5	NNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNYNNNNNN
EV005	0	57	1.22	13	2.6	6	NYNNNNNNNNN NNNNNNNNNNNNONNNNNNNYNNNNNNNNN
EV006	0	58	0.70	1	2.7	13	YNNNNNNYNYNNNN NNNNYNN ONNNNNNNNNNNYNNNN
EV007	0	53	0.82	1	2.5	6	YYNNNNNNNNNYNNNNNNNNNN ONNNNNNNNNNNYNNNN
EV008	1	60	0.48	1	2.7	13	YYYNNNNNNNNYNYNNNNNNNNNNNONNNYNNNNNNNYNNNN
EV009	1	64	0.66	1	2.5	15	NNNNNNNNNNNONNNNNNNNNNNYNNNN
EV010	0	62	0.66	1	2.5	6	NYNNNNNYYNNNNNNYNYNNNNYNONNNNNNNNYNYNNNNNNN
EV011	0	55	0.86	1	2.5	24	NNNNNNNNNNNNNNNNNNNNNNNNNONNNNNNNNNNNNNNYN
EV012	1	51	0.86	1	2.5	15	YYNNNNNNNNNYNYNNNNNNNYNNNONNNNNNNNYNNNNNNN
EV013	1	45	0.90	1	4.2	34	NNNNNNNNNY YNN NNNNNNN ONNNNNNNNNNN NNN
EV014	1	50	0.70	1	2.5	42	NYNNYNNYNNNNNNNNNNNNNNN ONNNNNNNNNNN NN
EV015	0	50	0.55	1	2.5	7	YYNNNNNNNNNNNYN NNNNNNN ONNNNNNNNNNNYNNNNY
EV016	0	53	0.55	1	2.5	5	NYNNNNNNNNNNNYN NNNNNNN ONNNNNNNNN YNNNNNN

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EV017	0	59	0.66	1	3.5	8	YYYNNNNNNNNNYYNNNNNNNNN .NNNNNNNNNNYNNNNNN
EV018	0	55	0.66	1	3.5	12	YYNNNNNNNNNN YN NNNNNNNNNONNNYYNNNNNNYNNNNNN

020	0	45	1.22	2	4.6	23	YYNNNNNNNNY NNN NNNNNNN ONNNNNNNNNNNYNNNNY
021	0	68	0.70	2	2.5	14	YYNNNYNNYYNNYNN NNNN NYNONNNYNNYNNNYNNNNNN
022	0	50	0.70	1	2.5	10	YYNNNYNN YNNNYNNNNNNNNNNN1YNNNNYNNNNN NN NN
023	0	58	0.94	1	5.0	14	YNNNNNNNNYYNNNNNNNNNN ONNNNNNNNNNNNNNNNN
024	1	68	1.12	1	2.5	84	YYNNNNNNYNYNYYN NNNNNNN ONNNYNNNYNYYNNNN
025	0	68	1.03	1	2.5	13	YYYNNNYYNNYNNNNNNNNNNN ,NN NNNNNNNYNNNNNN
026	0	53	0.78	2	3.8	10	YYNNNNNN Y NNNNNNNNNNN ONNNNNNNNNNYNNNNNN
027	1	69	1.12	2	2.5	15	YYNNYYNYYNYN N NNNNNNN ONNNNNYNNNYN YNN
028	0	48	0.90	2	2.5	9	NNNNNNNNNN NYNNNNNNNNNN ONNNNNNNNNNNYNNNNY
029	1	65	0.90	2	2.5	11	NYNNNNNN N NYN NNNNYNN ONNNNNNNNNNYNNNN
030	0	56	0.86	3	3.3	7	NNNNNNNNNY NNN YNNNNNN ONNNNNNNNNNYNNNNNN
031	1	65	1.62	19	2.5	15	NNNNNNNN NYNNN NNNNNNN ,NNNNNNNNNNNNNNN
032	0	51	1.12	4	2.5	7	YYYNNNNNNYNN NN YNNNNN ONNNNN NNNYNNNNNN
033	1	52	1.03	1	2.5	21	NYNNNNNNNNNYNYNNNNNNNNN ONNNNNNNNNNNYNNNN
034	0	60	0.99	1	2.5	6	NYNNNNNN NNN N NNNNNNN ONNNN NNNNNYYNYNNN
035	1	51	0.78	3	2.5	7	NNNNNNNNNNNNNNNNNNNNNN ONNNNNNNNNNNNNNN
036	0	64	0.90	3	2.5	9	YYNNNNNNNNNNNNNNNNNNNN ONNNNNNNNNNNYNNYNNN
037	1	56	1.12	4	2.5	16	NYNNNNNN Y NNN NNNNYNN ONNNNNNNNYNYN NNN
038	1	53	0.78	1	2.5	25	YNNNNNNNNNY NNNNNNNNNNN ONNNNNNNNNNNYNNNN
039	0	55	1.22	1	12.4	28	YYNNNNNNNNY NNN NNNNNNN ONN YNYNNNNYNNNNNN
040	0	58	0.92	1	2.7	11	YYNNNNNNNNNNNYN NNNNNNN OYNNNNNNNNNN NNNNN
041	0	59	0.86	19	2.5	19	YYYNYNNYNNNYNNNYYNNYNN ONNNNNNNNNNYYNNNNNN
042	1	54	0.92	3	2.5	38	NNNNNNNNNNNYNNNNNNNNNN ONNNNNNN YNYNNNN
043	0	55	0.98	4	11.0	8	YYYNNNNYNYNNYNNNNNNNNN ONNNNNNNNYNNYNNNNN
044	1	48	0.74	3	2.5	13	NNNNNNNNNNNYNNNNNNNNNYYYONNNYNNNNNNNNNN
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LE: EMASTER DATA A LEEDS UNIVERSITY VM/SP 2.05

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Raw Data Health Belief model Questionnaire

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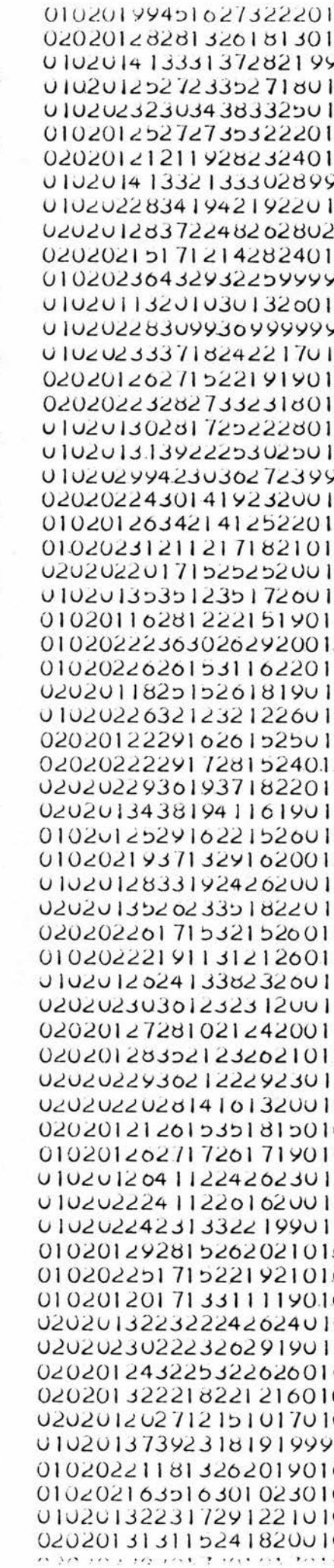

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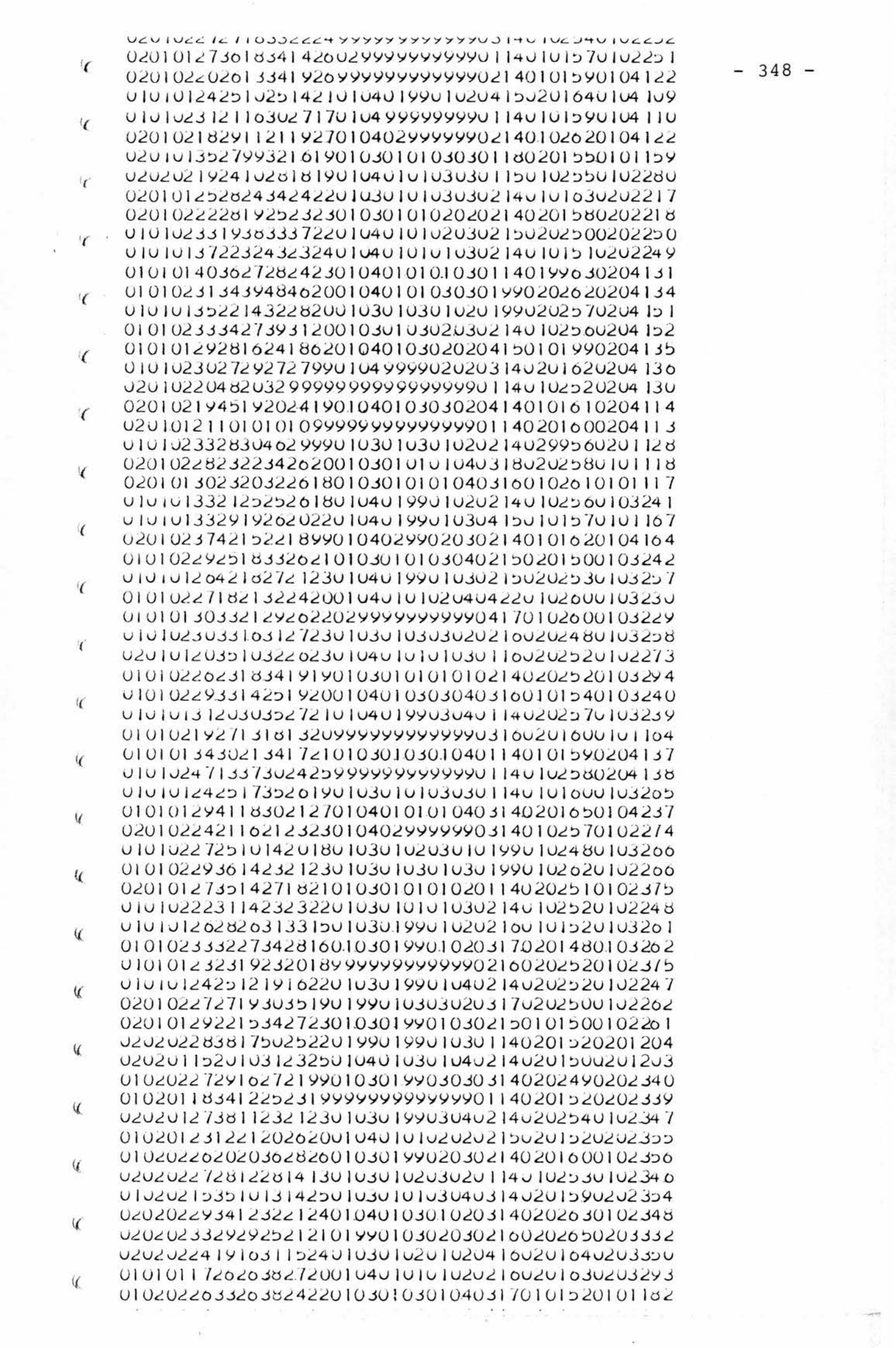

Br. J. Cancer (1986), **53**, 53–57

The role of a questionnaire and four biochemical markers to detect cancer risk in a symptomatic population

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Summary The roles of a self-completed symptom questionnaire and four biochemical markers of disease were assessed to determine risk for gastric and colorectal cancer from within a hospital population and a random population. Eight-six patients with cancer, 168 subjects with benign conditions of the stomach and large bowel and 720 individuals from the community at large were investigated. Multivariate analyses of the questionnaire and biochemical data were performed individually and in combination using a data set comprising 54 cancer subjects, 80 patients with benign disease and 200 random individuals. The most favourable predictive equation derived was then applied to the remaining data set to determine its efficacy. In the primary analyses the questionnaire data identified 32 (60%) cancers successfully and using the biochemical markers alone 36 (67%) patients were also correctly classified as cancer bearing. However, the combination of the questionnaire and marker data improved the sensitivity for cancer to 50 cancers detected (92%) ($P<0.02$). Using the predictive equation from this combination of data to identify risk in the second data set 28/32 (88%) cancers were correctly identified with only an 11% false positive rate. An 18 month follow-up for the non-cancer group has to date revealed only one cancer (ca. pancreas).

In this limited study, multivariate analysis of questionnaire and biochemical marker data does successfully identify individuals at 'high risk' of harbouring gastric or colorectal cancer within a symptomatic population and may have a role in determining priority for investigation for a symptomatic individual.

There can often be considerable delay in the diagnosis of gastrointestinal (GI) cancer in a symptomatic population presenting to a clinician, despite the availability of sophisticated methods of investigation (MacAdam, 1979; Holliday & Hardcastle, 1980). While it is desirable to investigate all symptomatic patients to exclude neoplasia, there has been a call to rationalise the way patients are referred for investigation, particularly to endoscopy units (Mann *et al.*, 1983). Clearly some simple method to select 'high risk' groups is required so that priorities for investigation of patients can be made and so reduce delay in the diagnosis of GI cancer.

Unfortunately no such simple method exists. Initially it was hoped that a serum tumour marker, such as carcinoembryonic antigen (CEA), would have sufficient sensitivity and specificity to detect GI cancer preoperatively in a symptomatic individual. The recent National Institute of Health Concensus Report (1981) declared that CEA should not be used as a preoperative investigative tool to detect GI malignancy and no other individual tumour marker has been found to be of value. However, the investigation of combinations of CEA and acute phase reactant proteins (APRPs) has shown that they may aid in prognosis for both gastric (Rashid *et al.*, 1982) and colorectal cancer (Ward *et al.*, 1977). This observation stimulated Chu and colleagues (1982) to assess the combination of CEA and alpha-l-acid glycoprotein pre-operatively in patients with colorectal cancer, where the sensitivity for detection of cancer increased significantly but was associated with a reduction in specificity. De Mello *et al.* (1983) pursued this approach by using a panel of six non-specific biochemical markers to define 'cancer risk' preoperatively; by applying multivariate analysis they identified 162 GI cancers (81%) with a false positive rate of 16%. Further, Walker and Gray (1983), applying discriminant analysis to a battery of markers found that the combination of serum protein hexose and CEA could significantly increase the preoperative detection of colorectal cancer. In addition Mann *et al.* (1983) have recently reported the use of multivariate analysis of the symptom complexes of patients presenting for endoscopy to develop a scoring index which identifies priority for investigation and 'risk' of upper GI disease.

We have incorporated both these approaches into a study to assess: (a) the use of multivariate analysis applied to four biochemical indicators of disease: CEA, gamma glutamyl transpeptidase (GGT), C-reactive protein (CRP) and alpha-l-acid glycoprotein (AGP) to identify cancer risk; and (b)

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Received 18 July 1985.

the role of symptom analysis with or without the addition of potential tumour markers to define risk for GI cancer.

Patients and methods

Eighty-six subjects with GI cancer, 168 with benign GI disease and 720 individuals from the general public were investigated (Table I). The group from the population at large was included since it has been shown by Jones (1976) and Thomson and Heaton (1979) that many apparently normal individuals may have present at any given time symptoms suggestive of significant gastrointestinal disease. Thus to produce a system to reduce over-investigation of individuals it is necessary to take account of the background prevalence of symptoms within an age-matched population. Entry into this group was determined by age, 50–70 years, and by enrolment by the general parctitioner of individuals felt to be free of active gastrointestinal disease.

Each individual was required to complete a symptom questionnaire and give a 10 ml sample of blood. The blood was allowed to clot, centrifuged at 3000 r.p.m. and the serum stored at −25°C for subsequent analysis.

Table I Details of study groups

Group	*No.*	*Mean age*	*Site of disease*
Cancer	86	68 y	57 Colorectal 29 Gastric
Benign	168	53.7 y	88 Colorectal disease 80 Gastroduodenal disease
'Normal'	720	58.1 y	No active GI disease

Questionnaire

The questionnaire comprised 41 questions, 18 relating to GI symptoms and 23 further questions pertaining to previous health, social history and pertinent epidemiological data. The format was simple, requiring a tick in a box to represent a positive or negative response. The questionnaire had previously been validated on 144 individuals and has been reported elsewhere (Chisholm *et al.*, 1985). In this survey only the 18 GI questions have been used in the subsequent analyses.

Analytical methods

CEA was determined using Phadebas CEA Prist kits supplied by Pharmacia Diagnostics AB (Upsala, Sweden). Gamma glutamyl transpeptidase (GGT) was measured at 37°C by the method of Haesen *et al.* (1972) using a Technicon II Auto-analyser. C-reactive protein (CRP) and alpha-l-acid glycoprotein (AGP) were measured by single radial immunodiffusion Mancini *et al.*, 1965) using anti-sera and standards obtained from Behringwerke, Marburg, Koln, Germany.

Statistical analysis

A preliminary analysis of the relative frequency of positive responses to each GI question was performed using a χ^2 test to detect significantly different response rates for cancer patients compared to the remaining groups. Similarly, the cumulative frequency distribution of each bio-chemical variable was plotted and, by using the 95th percentile value of the benign group as a cut-off point, the sensitivity and specificity of each marker to detect cancer were determined.

A logistic discriminant analysis (Anderson, 1972; Albert, 1982) has also been employed in this study to determine which variables are significant in discriminating between the cancer and non-cancer subjects. A stepwise procedure was adopted in which variables (4 tumour markers and 18 GI questions) are added to the model sequentially and at each step the statistical significance for each term not already in the model is calculated. The most significant variable at each step is added and when no variable is significant at the 5% level the process stops. Biochemical measurements underwent a logarithmic transformation (log 10) and positive responses to the questionnaire were accorded a score of +1 and a negative response −1. Sex was coded as +1 for male and −1 for female. The analysis was performed using the statistical package BMDP81, subroutine PLR, on the University of Leeds AMDAHL 470 computer.

To fit the model we used 54 cancer cases and the non-cancer group comprised 80 benign and 200 control population (first set data). As more cases were enrolled it was hoped that the model could be applied prospectively, thus permitting a more accurate impression of the validity of the model in a clinical setting (second set data).

Results

The sensitivity and specificity for the individual biochemical markers using an arbitrary cut-off point equal to the 95th centile of the benign group are shown in Table II. Thus the single most sensitive agent was CRP with an overall detection for cancer of 52%.

χ^2 analysis of the 18 GI questions revealed 6 questions which significantly distinguished between cancer and non-cancer subjects (Table III).

Table II Percentage of patients with a tumour marker value greater than the 95th centile of the benign group

Tumour marker	*Cut off value (95th centile benign)*	*Cancer (%)* *Colorectal*	*Gastric*	*Normal (%)*
CEA	$>10\,ng\,ml^{-1}$	47.4	48.3	2.5
AGP	$>1.4\,g\,l^{-1}$	36.8	65	2.6
CRP	$>12\,mg\,l^{-1}$	4.4	69	2.8
GGT	$>50\,U\,l^{-1}$	14	10	2.1

Table III Percentage frequency of positive responses per question for cancer and non-cancer groups

	Cancer	*Non-cancer*[a]	*P value (χ^2 test)*
Reduced appetite	56.7	29.78	0.0012
Weight loss	64.7	30.7	0.0001
Food sticking	33.3	24.6	0.0001
Nausea	24.0	42.0	0.02
Altered bowel frequency	71.9	37.8	0.0001
Altered stool appearance	62.7	36.7	0.0025

[a]Non-cancer = Patients with benign disease and normal individuals.

However 35% non-cancer bearing subjects had 3 or more positive responses present.

We used the first set of data to fit a logistic model to discriminate the cancer from the non-cancer group. Using only the biochemical data, 36 (67%) of the 54 cancer patients were correctly classified, with a false positive rate of only 5%. The 18 cancers missed by this simple discriminant included 5 patients with liver metastases from colorectal cancer and 2 patients with advanced gastric cancer. A similar analysis of the 18 GI questions correctly classified 60% cancers with a 5% false positive rate. In a logistic analysis using both the questionnaire and biochemical data, 50 cancers (92%) were separated from the non-cancer groups, with a similar 5% false positive rate (Table IV). This is a significant improvement on both the questionnaire and biochemical data when used individually ($P<0.02$, χ^2 test). The cancers missidentified were 2 colorectal cancers (Dukes' stage C+D) and 2 gastric cancers (stage II+IV).

Table IV Results of multivariate analyses applied to the initial data set

Variables	*Sensitivity ($n=54$)*	*Specificity (%)*
Biochemical markers	36 (67)[a]	95
Questionnaire	33 (60)	95
Markers plus questionnaire	50 (92)	95

[a]Percentage in parenthesis.

The fitted model is determined by the discriminant function (log to base 10): $y=0.605$ (sex) $+0.112$ (age) $+2.73$ log (CRP) $+5.33$ log (CEA) -4.09 log (GGT) $+1.05$ (wt loss) $+0.968$ (bowel habit) $+$constant (8.4) and the probability of cancer is then $P=\exp(y)/(1+\exp(y))$.

The 'optimal' cut-off point for these values to indicate cancer is $P\geqq 0.275$.

By applying this criterion to the second set data, 28 of 32 cancers (88%) were selected but the specificity fell to 89%. The 4 cancers misclassified as low risk for cancer were all colorectal (Dukes' C).

Application of this type of analysis to the patients with benign disease, lead to 26 of the 168 individuals being identified as at 'high risk' of cancer. However, included in the 26 there were 4 subjects with gastric ulcer or polyps and 4 patients with large colonic adenomata and villous polyps. Thus the system detected further 'high-risk' potentially premalignant conditions which clinicians would wish to investigate.

Fifty-six subjects of the 720 individuals in the GP study were classified by the analyses to be at high-risk for cancer. Only seven were investigated but no neoplasia was detected. In the remainder, raised acute phase reactant proteins (APRPs) due to upper respiratory tract infections (the reason for the GP consultation) may have caused the high probability value. To date, with a follow up of 18

months, no cancers have been identified in these 56 subjects.

Discussion

The problems of using a single tumour marker for cancer detection are again well demonstrated in this study. Even by taking the 95th percentile value of the patients with benign disease as the cut-off point for CEA detecting cancer, there is still 2.5% of the normal population with elevated CEA levels, whilst the sensitivity for cancer was only 47%. However, with a logistic analysis using the combination of four biochemical markers, we have confirmed the approach of de Mello *et al.* (1983) in that 36 (67%) cancers were detected in the first analysis, with a 5% false positive rate.

The analysis of the symptoms showed that 35% of the general population had at least three positive GI responses in the questionnaire. Eleven per cent had noticed rectal bleeding at some time (6% within a year) and 27% had experienced episodes of diarrhoea which somewhat dilutes these symptoms as potential markers for GI malignancy. Using the multivariate approach, only 60% cancers were correctly classified, thus showing the considerable overlap of symptoms between benign disease and cancer bearing subjects. This raises doubts concerning the validity of symptom complex analysis to determine cancer risk.

Combining the questionnaire data and the biochemical values, however, a significant improvement in the diagnosis of cancer has been achieved ($P<0.02$, χ^2 test). By demanding a cut-off point which assured a high level of specificity in the first data set, we feel that we have managed to reduce the degree of false positivity that would normally be expected in a second phase study. Thus the recognition of 88% cancers with an 11% false positive rate in the second data set using this method is encouraging. It could be argued that by accepting a low level of probability of cancer ($P<0.275$) we have ensured a high sensitivity. However, by utilising a large number of controls we have shown that few 'normal' individuals would be selected for investigation despite the presence of multiple symptoms in 30% of the population. Furthermore, few of the benign disease group (15%) would be selected for investigation, implying that the cut off is satisfactory. The classification of patients with gastric ulcers and polyps and colorectal polyps into the high risk group for cancer may be seen not as a failure of the system but potentially useful to recognise a 'pre-malignant' condition and would fit the significant disease category of Mann *et al.* (1983).

The follow up of the 26 subjects with benign disease who were labelled as 'high risk' has revealed one cancer already. This individual with upper GI symptoms who had negative barium meal and gastroscopy, but re-presented six months later, was found to have a carcinoma of the fundus of the stomach. The probability of cancer at the first presentation was 80% using the questionnaire and tumour marker data. We await with interest the outcome of those normal subjects who had a high probability and were not investigated subsequently.

Such results in a preliminary study must always be met with caution. Whilst the number of non-cancer subjects used in this study is larger than previous reports, the whole study is still small and we would envisage a rather prolonged prospective collection of data before evaluating the potential of this approach. Further to miss six potentially curable colorectal cancers and one curable gastric cancer is not to be considered lightly. However, all three symptomatic Dukes' A and 13 of 14 Dukes' B colorectal cancers were detected. We would stress that the objective is to identify 'risk' for cancer and therefore to define priority for investigation when dealing with a symptomatic population. Any patient with persistent symptoms could easily be referred sooner irrespective of the probability value.

The basic cost for this approach must be considered as a balance between expenditure on these tests *versus* any reduction in investigation costs by reduced referral rates. The biochemical analyses cost £5.00 per head (including labour but excluding overheads), the brunt of which is the price of the CEA kits. This could be offset by the reduction in unnecessary investigations where the probability of cancer is extremely low.

In conclusion, we would suggest that neither biochemical variables or symptom analysis alone will define 'cancer risk' as accurately as the combination of both in a multivariate analysis. We would cautiously recommend further interest and recommend this approach as a possible way of using resources to identify those symptomatic patients who should be fully investigated for cancer.

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STATISTICS IN MEDICINE, VOL. 4, 337–344 (1985)

HYPOTHESIS TESTING IN THE POLYCHOTOMOUS LOGISTIC MODEL WITH AN APPLICATION TO DETECTING GASTROINTESTINAL CANCER

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SUMMARY

We discuss the use of the trichotomous logistic model to discriminate between patients with gastrointestinal(GI) cancer, patients with benign GI disease and 'normal' subjects, using symptoms and the concentrations of some serum proteins that are potentially indicative of malignancy as covariates. A parsimonious model can be obtained by invoking an indistinguishability hypothesis which is appropriate when a covariate is considered to have no predictive value between categories. It is shown that the polychotomous model can be re-parameterised under the null hypothesis to give a 'reduced form', which can be fitted by maximum likelihood. The validity of the use of the same methods for retrospective sampling is discussed. The approach is illustrated by the development of a logistic model to identify symptomatic and asymptomatic subjects with a high risk of GI cancer.

KEY WORDS Logistic model Indistinguishability hypothesis Gastrointestinal cancer Maximum likelihood

INTRODUCTION

The dichotomous logistic regression model is now widely employed in medical research but there are only a few cited examples[1] where the polychotomous logistic regression model has been used, even though it has advantages over normal theory discriminant analysis[2]. In this paper we describe an application of the use of a trichotomous logistic model to identify subjects with a high risk of gastrointestinal (GI) cancer using the concentrations of certain serum proteins and GI symptoms as covariates. The number of parameters to be estimated, $(p+1)(k-1)$ for p covariates and k categories, may be excessive for a parsimonious representation and methods of achieving a more economical model are desirable. One approach is to consider formulating hypotheses concerning the predictive value of covariates in the model. Anderson[3] has used the term 'indistinguishability' to describe a hypothesis of this sort, a terminology that we shall also adopt. Under the null hypothesis the polychotomous model can be written in a 'reduced form'. By fitting the reduced model it is possible to test the null hypothesis with either a score test or a Lagrange multiplier test[4], or if the full model is also fitted, with the likelihood ratio test. It has recently been shown that it is possible to carry out a polychotomous logistic analysis by fitting a number of separate dichotomous models

0277–6715/85/030337–08$01.00 *Received September 1984*

with little loss of efficiency[1,5]. However, this approach is not generally appropriate for the reduced form of the logistic model that we consider in this paper. Software for fitting the reduced model is also not readily available and we have accordingly developed a suitable program ourselves. We now outline the background to the study that stimulated this work.

THE GASTROINTESTINAL CANCER STUDY

There is often a considerable delay between the onset of symptoms and the diagnosis of GI cancer. Many patients are diagnosed with advanced disease and the tumour stage at diagnosis is sometimes associated with the duration of this delay[6]. A number of factors may contribute to a delay; initially immediate action might not be taken because many of the early symptoms are also indicative of benign or relatively minor conditions. Persistent symptoms usually lead to referral for specialist treatment, which might necessitate exploratory tests such as endoscopy, and possibly also surgery. These procedures are time consuming and expensive and often prove to be negative for cancer. Consequently there is a need to determine a system of priorities to select symptomatic patients for investigation. Similarly, there are obvious benefits if subjects with a high risk of GI cancer could be isolated prior to the onset of symptoms. Clearly some simple methods to isolate high risk subjects are desirable.

The role of biochemical markers in screening, diagnosis and monitoring of cancer of the GI tract has been discussed widely in the literature[7]. In particular the serum protein carcinoembryonic antigen (CEA) has been considered a promising marker of malignancy but its lack of specificity has precluded its widespread use[8]. The combination of a number of serum proteins has been suggested for detecting GI cancer pre-operatively in symptomatic patients (De Mello *et al.*[9]). These authors claimed an 84 per cent sensitivity and an 81 per cent specificity with a dichotomous logistic regression model to discriminate between patients with GI cancer and patients with non-malignant GI disease, but they did not consider including symptoms in their model. One stimulus for the present study, therefore, was to investigate whether serum proteins together with symptoms might provide a better model. We also felt that the inclusion of 'normal' subjects in the study would be useful in that it would give an indication of the background prevalence of symptoms and of 'normal' concentrations of the serum proteins. Three groups were therefore considered for the study: patients with GI cancer, patients with benign GI disease requiring endoscopic investigation, and apparently 'normal' subjects aged over 45. Separate samples of the cancer and benign GI groups were taken from patients referred to the Department of Surgery, St James's University Hospital, Leeds. The benign group included symptomatic patients undergoing therapy for a non-malignant condition, and the cancer group consisted of a consecutive sample of patients with a confirmed diagnosis of cancer of the oesophagus, the stomach or the large bowel. The normal sample was collected over a period of eighteen months from six general practice clinics in the Leeds area. Patients attending with a GI complaint or with a history of GI disorders were excluded. Each patient supplied a blood sample from which CEA and three other tumour associated serum proteins were measured immunochemically: gamma-glutamyl transpeptidase (GGT), alpha$_1$-acid glycoprotein (AGP) and C-reactive protein (CRP). In addition patients completed a questionnaire, from which 14 binary responses relating to key GI symptoms were derived (Table I). Complete data for a total of 96 cancer patients, 163 benign patients and 804 normal patients were obtained. Only 100 normal patients and 99 benign patients were used for model development, the remaining patients were set aside for model validation. Further details relating to the clinical aspects and the motivation for the study are discussed by Chisholm *et al.*[10].

The objective was twofold: first to consider whether symptoms and protein concentrations could be used to distinguish between benign and cancer patients in a symptomatic population, and,

Table I. A list of the 14 gastrointestinal symptoms in the questionnaire

Symptom	Description
1	Recent weight loss
2	Recent appetite loss
3	Food sticking before reaching stomach
4	Burning or discomfort behind breastbone
5	Nausea or vomiting
6	Pain or discomfort in abdomen
7	Abnormal frequency of motions*
8	Need to go after emptying bowels
9	Altered bowel habit
10	Change in motion appearance
11	Periods of loose motions
12	Motions becoming more constipated
13	Blood in motions
14	Slime in motions

* More than 3 per day or fewer than 3 per week.

second, to determine the usefulness of these factors for a cancer 'case finding' role in an asymptomatic population. Separate dichotomous logistic regression models between the benign and cancer groups and between the asymptomatic and cancer groups can be contemplated, however, we considered that a more satisfactory analysis, in view of the three distinct categories, might be obtained by fitting a trichotomous logistic regression model between all three groups. From such a model the individual logistic models between each of the three pairs of categories can be derived, and the trichotomous form allows classification to a benign, possibly pre-malignant, state. Readers not interested in the mathematical details of the polychotomous logistic model should omit the next section.

THE REDUCED LOGISTIC MODEL

Suppose that Y is a multinomial variable with a sample space of k possible categories $\{y_1, \ldots, y_k\}$ and that $\mathbf{x} = (x_1, \ldots, x_p)$ is a vector of covariates. The logistic model specifies a conditional probability for Y given $\mathbf{x}$ of the form

$$p_{sx} = p(Y = y_s|\mathbf{x}) = \frac{\exp(\mathbf{X}\boldsymbol{\alpha}_s)}{\sum_{t=1}^{k} \exp(\mathbf{X}\boldsymbol{\alpha}_t)} \tag{1}$$

where $\mathbf{X} = (1, \mathbf{x})$ and $\boldsymbol{\alpha}_s = (\alpha_{s0}, \ldots, \alpha_{sp})^{\mathrm{T}}$ is a vector of model parameters, α_{s0} being a constant term. For uniqueness it is assumed that $\boldsymbol{\alpha}_k = \mathbf{0}$. Often it may be of interest whether a particular covariate, say x_j, has any potential for discriminating between categories y_t and y_s. To be specific we can consider categories y_s and y_t to be 'indistinguishable' with respect to a covariate x_j when $\alpha_{sj} = \alpha_{tj}$ or, equivalently, when the relative risk of y_s against y_t, for a given $\mathbf{x}$, does not depend on x_j. More than two categories may be indistinguishable so that, defining a set of categories S_j for x_j, a null hypothesis is

$$H_{0j}\text{: } \alpha_{sj} = \alpha_{tj} = c_j \text{ for } y_s \text{ and } y_t \text{ belonging to the set } S_j.$$

Here c_j is not specified unless y_k is included in S_j and then $c_j = 0$, since $\boldsymbol{\alpha}_k = \mathbf{0}$. A null hypothesis H_{0j}

can be defined for any number of covariates and a compound null hypothesis, H_0, can be constructed from the separate hypotheses for each such j. The term $\exp(c_j x_j)$ can be factored from the numerator and denominator of (1) and the model reparameterised with $\alpha_{sj} - c_j$ replaced by α^*_{sj}. Under H_{0j}, $\alpha^*_{sj} = 0$ for y_s belonging to the set S_j so the model under H_0 can be written as

$$p_{sx} = \frac{\exp(\mathbf{X}_s \boldsymbol{\beta}_s)}{\sum_{t=1}^{k} \exp(\mathbf{X}_t \boldsymbol{\beta}_t)} \tag{2}$$

where $\mathbf{X}_s$ is a vector of length q_s consisting of the elements of $\mathbf{X}$ that correspond to the non-zero α_{sj}, and $\boldsymbol{\beta}_s$ is a vector of corresponding model parameters. Henceforth (2) is referred to as the 'reduced logistic model' under H_0. If Q_s denotes the index set of covariates referenced in $\mathbf{X}_s$ then (2) is unique in its parameters if the intersection of Q_s over $s = 1, \ldots, k$ is null. The approach to fitting the logistic model by fitting separate dichotomous models[4] is not appropriate unless one of the Q_s sets is empty, so that there is a pivotal category. The simple case $k = 3, \mathbf{X}_1 = \mathbf{X}_2 = (1, \mathbf{x}_1)$ and $\mathbf{X}_3 = \mathbf{x}_2$ illustrates this: the parameter $\boldsymbol{\beta}_3$ appears in the individual regressions between categories 1 and 3, and between categories 2 and 3.

An advantage of the parameterisation in (2) is that it has the same structure as the unrestricted model (1) so that any program that is used to fit (2) can be used to fit both the restricted and unrestricted models. The maximum likelihood equations for fitting (2) when sampling is prospective, that is when observations of Y given $\mathbf{x}$ are made, are similar to those given for example by Anderson[2] and are omitted. A solution can be obtained by a Newton–Raphson procedure and this is the method that we have adopted in our program. Possibly other accelerated convergence algorithms would be faster but we have found Newton–Raphson quite efficient and the estimated information matrix is obtained directly. With minimal extra programming the Lagrange multiplier test statistic[4] can also be computed. This test asks whether the restricted estimates are sufficiently near to the absolute maximum of the likelihood. (It is computed as a quadratic form $\mathbf{1}_0^T \mathbf{L}_0 \mathbf{1}_0$ where $\mathbf{1}_0$ is the first derivative vector and $\mathbf{L}_0$ is the second derivative matrix of the likelihood with respect to the parameters in the unrestricted model, but computed with the restricted estimates.) Copies of the computer program are available on request.

When sampling is retrospective, that is, when separate samples are taken from each of the k categories and $\mathbf{x}$ is the observed variable, the inference problem is less straightforward[2,11–13]. For model (1) it is, however, legitimate to treat the sample as if it were obtained prospectively and to make adjustments to the constant term estimates according to the prior probability, p_s, and sample size, n_s, associated with each category. Specifically this means adding $\log(n_k p_s / n_s p_k)$ to the estimated constant terms. This theory carries over to the reduced model (2) if the model includes precisely $k - 1$ free constant terms.

RESULTS FOR THE GI CANCER STUDY

As outlined above the GI study data consisted of separate samples from three populations: cancer, benign and 'normal' patients. It is therefore necessary to invoke the retrospective theory mentioned above. Since the serum protein values are continuous variables the resulting estimates are not maximum likelihood in the strict sense[2,11]. In practice however, they may be treated as such and the usual likelihood theory for testing the model, treating the retrospective sample as if it were a prospective one, can be utilised. We require, however, a prior probability for each category to 'adjust' each constant term. To classify an apparently normal individual, a prior probability should reflect the prevalence of pre-clinical cancer and benign disease in the population. Prevalence rates are not easily obtained but the incidence of cancer is well recorded[14], as is the incidence of benign

disease requiring in-patient treatment[15]. Simple calculations show an incidence of GI cancer of about 4 per 1000 for the population aged 45 and over[14], and the in-patient treatment rate for benign disorders is 3·8 per 1000 for the same age group[15]. The majority of benign disorders are, however, treated as out-patients. Experience at endoscopy units in Leeds suggest that about 1 of every 10 cases in the elderly age group that is diagnosed with a GI disorder has cancer. If the incidence rate for cancer is also adopted as a measure of prevalence, prior probabilities of 0·004 and 0·036 are suggested for cancer and benign disease respectively. These are the figures that we have adopted for subsequent analysis. It is, however, legitimate to use subjectively chosen prior probabilities for the classification of an individual.

The four serum proteins and the 14 questionnaire responses, together with sex and age, give a total of 20 covariates and 42 parameters for the unrestricted trichotomous logistic model. A model with fewer parameters was felt to be desirable and two hypotheses were thought to be feasible: first, that the benign and cancer patients are indistinguishable with respect to the questionnaire responses and, second, that the benign and normal groups are indistinguishable with respect to the serum proteins. These two hypotheses will be referred to as H_Q and H_S respectively and H_0 is used to denote both H_Q and H_S. Various authors[5,16,17] have given evidence to support H_Q, at least for early stages of GI disease, and the potential role of the serum proteins as markers of malignancy justifies consideration of H_S.

It is instructive to demonstrate the construction of the appropriate reduced model to test H_0. If the covariate vector $\mathbf{x}$ is partitioned as follows

$$\mathbf{x} = (\mathbf{x}_0, \mathbf{x}_Q, \mathbf{x}_S),$$

where $\mathbf{x}_0$ is the vector of age and sex, $\mathbf{x}_Q$ is the questionnaire vector, and $\mathbf{x}_S$ is the serum protein vector, then under H_0 the reduced form (2), with $s = 1, 2$ and 3 referring to the cancer, benign and normal groups respectively, can be written with

$$\mathbf{X}_1 = (1, \mathbf{x}_0, \mathbf{x}_S); \quad \mathbf{X}_2 = (1, \mathbf{x}_0); \quad \mathbf{X}_3 = \mathbf{x}_Q.$$

Table II gives the likelihoods attached to each of the fitted models with the associated likelihood ratio and Lagrange multiplier test statistics. The test for H_S is not significant, whilst the tests for H_Q and H_0 are inconclusive. Consequently we considered it wise to adopt H_S but to test an alternative hypothesis concerning the questionnaire data in which only certain questions were considered indistinguishable between the cancer and benign categories. Chi-square tests for differences in response rates were used to indicate which questions might be indistinguishable, and an appropriate reduced model was fitted in which the non-significant responses were made indistinguishable. This reduction was not significant ($P = 0{\cdot}53$). A further reduction in the model was obtained by a 'manual' stepwise procedure in which estimates were compared with their estimated standard errors and those not significant were removed. The effect of the reduction at each step was judged by the likelihood ratio test. This led to a model with 15 parameters (Table III). No further reduction seems feasible though a number of possibilities have been tried. The serum proteins CRP and GGT do not add anything to the model and only 6 questions are useful, 3 of these, Q3, Q5 and Q14, being indistinguishable between the cancer and benign groups.

The model can be used in two ways: first to identify cancer patients in a symptomatic population and, second, to pick up subjects with GI disease prior to the onset of symptoms. For the former a dichotomous logistic model, between cancer and benign patients, can be derived directly from Table III. To use the model for 'case finding' one can calculate the probability of both cancer and benign disease using the trichotomous form, and isolate likely cancer cases as well as likely benign cases, since these may be indicative of a pre-malignant condition. We now briefly give some results on the predictive accuracy of the model.

Table II. The log-likelihoods associated with the unrestricted model and with alternative reduced models

Model	No. of parameters	Maximum log-likelihood	Likelihood ratio test	Lagrange test	D.F.	*p*-value
Unrestricted	42	−135·90	—	—	—	
H_Q	28	−150·15	28·50	25·17	14	0·02
H_S	38	−137·54	3·64	3·10	4	0·50
H_0	24	−151·68	31·56	28·26	18	0·03
Final model (Table III)	15	−150·26	28·72	26.27	27	0·60

H_Q = indistinguishability of cancer and benign groups with respect to questionnaire data; H_S = indistinguishability of benign and normal groups with respect to serum proteins; H_0 = both H_Q and H_S. *P*-values are obtained using the chi-square approximation for the likelihood ratio test.

Table III. The covariates and their associated estimated values for the 15 parameter reduced model

Cancer ($n_1 = 96$)		Benign ($n_2 = 99$)		Normal ($n_3 = 100$)	
Age	0·092 (0·02)	Q1	1·407 (0·59)	Q3	−1·173 (0·53)
Sex	1·817 (0·52)	Q2	2·343 (0·82)	Q5	−1·607 (0·44)
AGP	1·846 (0·55)	Q9	2·047 (0·57)	Q14	−2·504 (0·58)
CEA	0·325 (0·07)	Constant	−1·581 (0·26)		
Q1	2·186 (0·77)	Constant*	−4·854		
Q2	3·306 (0·96)				
Q9	3·728 (0·72)				
Constant	−13·894 (1·89)				
Constant*	−19·358				

* 'Adjusted' for separate sampling using prior probabilities 0·004 and 0·036 for cancer and benign disease respectively.

Figures in parentheses are estimated as asymptotic standard errors. All covariates are binary (1 = yes) with the exception of AGP (g/l), CEA (μg/l) and Age (years).

Q1 = weight loss; Q2 = appetite loss; Q3 = food sticking; Q5 = nausea or vomiting; Q9 = altered bowel habit; Q14 = slime in motion; Sex = 1 for male.

Consider first using the model for 'case finding'. High risk individuals can be isolated if their estimated cancer probability exceeds c_1 or, when this criterion fails, if their benign probability exceeds c_2. A system of utilities might be used to optimise the choice of c_1 and c_2; here we discuss only the sensitivity for some arbitrarily chosen values. One possibility is to take c_1 and c_2 equal to the prior cancer and benign probabilities, 0·004 and 0·036. In this case, for the 295 patients that were used to fit the model, 93% (89/96) of cancer patients, 45% (45/99) of benign and 79% (79/100) of asymptomatic patients were correctly classified. However, the probability of actually having cancer *given* classification to the cancer group, which can be computed from these empirical classification rates and the prior probabilities by using Bayes Theorem, is only 0·15 and the corresponding figure for benign disease is 0·08. The low predictive accuracy results from the low prevalence of cancer together with an estimated 0·01(1/100) misclassification rate from normal to cancer and a 0·02(2/100) misclassification rate from normal to benign. This problem with predictive accuracies is well known[18]. If c_1 and c_2 are both increased to 0·5 there are no misclassifications of the normal group to cancer and the estimated probability of having cancer, when being assigned to cancer, is

now more acceptable at 0·86. The corresponding figure for benign disease is still low at 0·43. However, only 54% (52/96) of cancer patients and 21% (21/99) of benign patients are correctly classified although 99% (99/100) of the normal cases are correctly classified. It is instructive to consider how the model fares on the group of 704 asyptomatic patients set aside for model validation. Follow up studies of these patients, using faecal occult blood (FOB) tests and exploratory tests for the patients with a positive FOB response, have identified one case of sigmoid cancer and three cases of benign polyps. Unfortunately none of these cases gave an abnormally high probability of either cancer or benign disease. Using the $c_1 = c_2 = 0{\cdot}5$ rule there were no classifications to cancer and 16 classifications to the benign category. Only 4 of these cases have, to date, been diagnosed with a GI disorder. These results raise doubts as to the use of the model to identify disease in an asymptomatic population. Consider, however, classification for a symptomatic population. If the dichotomous model between the cancer and benign states is derived from Table III and is used to classify symptomatic patients, then 59% (57/96) of cancer patients and 98% (97/99) of benign patients are correctly classified, adopting a cutoff probability of $c = 0{\cdot}5$, that is, assign to cancer if the estimated probability of cancer exceeds c. The probability that a patient who is assigned to the cancer group actually has cancer is 0·76. The corresponding figure for benign disease is 0·96. Alternatively for $c = 0{\cdot}1$ these probabilities are 0·47 and 0·99 whilst for $c = 0{\cdot}9$ they become 1·0 and 0·94. The value 1·0 arises with $c = 0{\cdot}9$. because there are no misclassifications from benign to cancer, but only 41% (39/96) of the cancer patients are correctly classified. With the $c = 0{\cdot}5$ rule, 63 of the 64 benign patients that were set aside for validation were correctly classified to the benign state.

CONCLUSION

These results demonstrate that it is feasible to use the model for detecting malignancy among symptomatic subjects, but it will require further testing to establish its usefulness for routine work for an asymptomatic population. It was always doubtful whether the model would perform well for asymptomatic cases, since symptomatic patients were used for its development and it is being required to detect patients at a preclinical stage. Nevertheless, the concept of using both symptoms and a set of biochemical tests to define high risk subjects seems worth persuing, possibly with alternative 'tumour markers' and a more comprehensive description of symptoms. The framework of the logistic model is suitable for work of this sort and the 'reduced form' is particularly useful for constructing tests concerning the predictive value of covariates.

ACKNOWLEDGEMENTS

We would like to thank the referees for their useful comments on an earlier draft of the paper. We wish also to acknowledge the support of Yorkshire Cancer Research Campaign and the Yorkshire Regional Cancer Organisation.

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Reprinted from the **BRITISH MEDICAL JOURNAL**, *15th June 1985, 290, 1795-1796*

Validation of a self administered questionnaire to elicit gastrointestinal symptoms

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Abstract

Self administered questionnaires are becoming popular investigative tools in medical research, yet few reports state the extent of methods used to validate these questionnaires before their general use. A pilot study was therefore carried out to validate a 41 item questionnaire for use in a population screening study for gastrointestinal disease.

Participants in the study comprised 69 population controls, 40 patients with benign disease, and 35 patients with gastrointestinal cancer. Acceptability, ease of completion, reliability, and reproducibility of the questionnaire were all assessed. Only one subject refused to complete the questionnaire. Ninety six per cent of the questions were completed by each subject and only one response in 1440 was altered in the reproducibility study. The questionnaire disclosed symptoms similar to those elicited by a clinician and highlighted unreported gastrointestinal symptoms in the control group. Three questions were found to be unreliable and were altered before the questionnaire was put into general use.

It is concluded that a pilot study to validate a new questionnaire is simple to perform and necessary to identify unreliable questions.

Introduction

Self adminstered health questionnaires have been used as an adjunct to medical history taking for many years,[1] but more recently questionnaires have been seen as investigative tools to identify risk groups for cardiac disease,[2] colorectal neoplasia,[3 4] and upper gastrointestinal disease.[5] Few questionnaires, however, have been subjected to critical statistical analysis to determine their validity before being used clinically.[6] To be valid a questionnaire needs to meet five criteria: (*a*) to be acceptable to the population under study; (*b*) to be easily completed; (*c*) to be consistent—that is, to elicit responses similar to those gained in a conventional doctor-patient interview; (*d*) to be reproducible when administered on two separate occasions; (*e*) to be of value or use when complete.

We report the steps taken to validate a questionnaire to elicit gastrointestinal symptoms in a screening programme for bowel cancer.

Questionnaire

The questionnaire contained 41 questions. Eighteen were specifically related to gastrointestinal symptoms—oesophagus (3), stomach (3), bowel habit (8), weight and appetite (4)—and the remainder covered epidemiological data (4), previous medical history (6), family history (2), and a general systems inquiry (11)—respiratory system, genitourinary system, and drug usage. The questions were closed in nature and it was possible to omit five responses if negative answers were given to the preceding question. To answer a question a tick was placed in the appropriate yes or no box.

Patients and methods

A total of 144 subjects were enrolled and were divided into three groups: 69 "normal" subjects who were not attending hospital; 40 patients with proved benign gastrointestinal conditions; and 35 patients with proved gastrointestinal cancer. All 144 subjects were required to complete the form unaided in order to assess the acceptability and feasibility of completing the questionnaire. A test-retest system was used to assess the reproducibility of the responses, 20 subjects being required to complete a second questionnaire after a two week interval.

Twenty three patients with symptoms referred to hospital by their general practitioner completed a questionnaire before being interviewed in the routine manner by a consultant. To determine the consistency of the responses on the patient's questionnaire the clinician then completed an identical questionnaire on the basis of the interview and without reference to the patient's form. The two forms were then compared using kappa statistics.

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BMJ/1140/85

Statistical method—Since the possibility of chance agreement between two series of replies to the same set of questions varies according to the incidence of positive and negative replies to the individual questions, the kappa statistic was calculated to adjust for the contribution of chance agreements.[7] Kappa (k) is calculated according to the formula, $K=(Po-Pe)/(1-Pe)$, where Po is the observed proportion of agreement and Pe is the proportion of expected agreement from chance and calculated from the marginals in a two by two table. The values for kappa vary from 1·0 where there is total agreement to −1 where there is total disagreement. A value of zero corresponds to chance agreement alone.

Results

Acceptability—One subject refused to complete the questionnaire.

Feasibility—Three subjects failed to complete the questionnaire owing to poor eyesight or dyslexia. The average time for completion was seven minutes (range four to 10 minutes). The completion rate for the questionnaire was 96% of all questions.

Reproducibility—In all three groups the test-retest study showed that only one answer was altered in one questionnaire, and this related to family history. Thus only one response was changed out of a possible 1440 answers.

Consistency—In the study which compared responses obtained on the questionnaire with those obtained by the consultant clinician kappa statistics were applied to the 18 gastrointestinal symptoms. In 15 questions there was a close correlation of answers and all the kappa values exceeded 0·85. With three questions, however—namely, those designed to elicit responses concerning tenesmus, early satiety for food, and new episodes of abdominal pain—the kappa values were 0·2, 0·125, and 0·3 respectively. The remaining general questions all had kappa values of 1.

Applicability—When the responses to the gastrointestinal questions were compared among the three groups of subjects the number of positive responses was naturally greater in the hospital referred groups. Of 65 subjects in the normal group, 54 (83%) had zero or one positive response, seven having three or more positive responses. In the group with cancer 33 of 35 (94%) had three or more positive responses, as did 33 of the 40 subjects (83%) in the benign disease group (table). Follow up assessment of the seven

Distribution of positive gastrointestinal responses in three groups

No of positive responses	Normal (n=65)	Benign (n=40)	Cancer (n=35)
0	39	0	0
1	15	3	0
2	4	4	2
≥3	7	33	33

"normal" patients showed that one had a confirmed diagnosis of ulcerative colitis, two were treated for dyspeptic symptoms on follow up, and three were referred for investigation of rectal bleeding and were found to have haemorrhoids. The remaining subject, who had right sided abdominal pain, loose altered stool, and altered urine colour, was found to have stones in the common bile duct on investigation.

Discussion

The format and content of the questionnaire were clearly acceptable to the population sampled. The high degree of compliance recorded, however, may have been biased by small sample size. Problems in completing the questionnaire would probably occur commonly if the questionnaire were applied to the population at large, owing to embarrassment, lack of reading glasses, and illiteracy.

The benefit of the realiability section of the pilot study was to identify those questions that were unreliable before general use. The phraseology of these questions was identical with that used in previous questionnaires and structured interviews,[1 3 5 8] and their apparent failure in our specific study reinforces the view put forward by Oppenheim that merely using questions from other questionnaires without testing them in the context of their eventual use cannot be justified.[9]

By using the test-retest assessments and the correlation study we were able to observe the ability of the questionnaire to elicit symptoms successfully both in the known symptomatic groups and also in the supposedly normal population group, leading to the detection of previously unsuspected gastrointestinal disease. Furthermore, and equally important in the screening setting, a negative response to gastrointestinal questions was found to be a true negative response in all 15 reliable questions, and on retesting no negative gastrointestinal response became positive. These findings are consistent with other data on reproducibility studies of health questionnaires.[6 10]

The questionnaire accurately elicited symptoms of gastrointestinal disease in the hospital group, and on subsequent follow up of the heavily symptomatic "normal" group further disease was identified, so the potential value of the questionnaire can be seen. This is shown in the table below where the distribution of positive responses is analysed by group. Here the risk of gastrointestinal disease and therefore the potential need for investigation can be defined. In the case of this particular questionnaire the risk is defined by three or more positive responses.

We conclude that a pilot study of any questionnaire is mandatory to identify any faults in its format or content; that it takes little time or effort to perform; that simply using questions from established health questionnaires does not imply reliability; and that statistical methods should be applied to the correlation studies to ensure the validity of the questionnaire.

By performing our pilot study we have devised a questionnaire that can reliably elicit symptoms of gastrointestinal disease consistent with the ability of a clinician but can also accurately identify people with established gastrointestinal disease and can highlight normal subjects with symptoms, as yet unreported to a doctor, that merit further investigation.

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(Accepted 28 February 1985)

Printed in Great Britain by Bourne Offset Ltd., Iver, Bucks.

THE COMBINATION OF SELF-ADMINISTERED SYMPTOM QUESTIONNAIRE AND FAECAL OCCULT BLOOD TESTING IN COLORECTAL CANCER SCREENING

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ABSTRACT

The faecal occult blood test (FOB) has several limitations including high false positive rates, high false negative rates and low compliance, which reduce its validity as a screening agent for colorectal cancer. We have investigated the use of a self-administered general health questionnaire in conjunction with FOB testing in 1082 subjects to assess the value of the questionnaire to screen for colorectal neoplasia and compared its acceptability and yield of neoplasia with that of the FOB test. 720 (66.6%) individuals completed the questionnaire whilst 689 (63.7%) completed the FOB test. 20 FOB tests were positive and upon investigation 5 subjects were found to have neoplastic lesions -2 cancers and 3 large polyps. This represents a predictive yield for a positive FOB as 25%. 29 subjects were investigated for symptoms alone but none were found to have evidence of large bowel neoplasia (0% yield). The questionnaire significantly increased the false negative investigation rate and precludes its routine use in colorectal cancer screening.

INTRODUCTION

For the past 2 decades, the crude 5 year survival rate for colorectal cancer, the second commonest cancer in the UK, has remained at 21%[1]. Since the reported survival of early stage cancer may be 65% -88%[2,3] a great deal of research has been directed into the use of screening agents to detect these early lesions. The screening agent most commonly used is the faecal occult blood test (FOB), Haemoccult (Eaton Laboratories), but the agent has certain severe limitations of its use. These include a high false positive rate[4], a high false

negative rate for symptomatic cancer[5], polyps[6] and asymptomatic cancer[7] and an extremely low acceptability to the population of the UK[8,9]. Alternative methods for screening to aid the FOB's validity have been sought and recently the use of a symptom questionnaire was advocated by Schewe[10] to identify the symptomatic cancer patient with a false negative FOB. Silman et al[11] have reported a study which combined the FOB with a 9 item questionnaire, and noted that "all significant neoplastic lesions detected on screening were symptomatic" and were thus detected by the questionnaire. Further they stated that the predictive yield for a positive questionnaire was statistically indistinguishable to that of the FOB test. Crespi[12] has reported similar findings using a 4 item questionnaire where a positive neoplastic yield of 16% on investigation of a positive response was noted. Since a questionnaire is simple and easy to complete it would overcome the natural reluctance of the population to perform FOB testing and may therefore be a more viable form of population screening.

We have therefore investigated the use of a questionnaire in a colorectal cancer screening study where the yield of neoplastic disease discovered by the questionnaire was to be determined and compared with conventional FOB testing.

PATIENTS AND METHODS

1082 subjects, from 6 group practices, were invited either directly by their general practitioner during a consultation or by a letter to participate in the study. Each individual was in the age range 50-70 years and had to have no active gastrointestinal (GI) complaints or be on active GI therapy at the time of entry to the study.

A 41 item questionnaire (Table 1), specially designed for the

study and previously validated[13] was completed by the subject. The questionnaire contained 18 specific GI questions and the format was a simple one requiring a tick in a box for yes or no. Any individual with 3 or more positive symptoms (as determined by the previous pilot study) was reviewed and investigated where indicated. Counselling on FOB testing was then given and a completed 3 day package was then returned by post for testing by the same individual (EMC). A positive FOB was investigated by fibreoptic sigmoidoscopy and either double contrast barium enema or colonoscopy.

RESULTS

720 individuals completed the questionnaire, whilst 689 subjects completed the FOB test. 20 individuals (2.9%) had one or more FOB slides positive, none of whom had a positive response to the GI symptoms. Investigation of these subjects lead to the discovery of 2 colonic cancers (1 Dukes' A descending colon; 1 Dukes' B sigmoid colon) and 3 adenomatous polyps greater than 1 cm diameter in 5 individuals. This represents a predictive yield for neoplasia for a positive FOB of 25%.

240 subjects (35%) had three or more positive responses to the questionnaire. In the analysis, it became clear that many apparently normal individuals suffered from symptoms attributable to the upper gastrointestinal tract e.g. heartburn 24%, nausea 13%. As our principle concern was directed to a study of large bowel disorders, these individuals are excluded from this analysis which concentrates on symptoms normally associated with colonic disorders. Table II shows the distribution of positive responses for the total group to the questions concerning the GI tract. Whilst 77 (11%) had noticed fresh blood per

rectum only 42 (6%) had noticed this in the previous 6 months and only 5 (0.8%) had not already reported the symptom to their general practitioner. Similarly, 26% reported periodic diarrhoea and 14% reported constipation. In view of the widespread prevalence of these general symptoms it proved necessary to re-examine the questionnaire data. Consequently, after further consultation only 29 individuals (4.2%) underwent definitive investigation of the large bowel. In this group, no neoplastic conditions were identified, although disease was recognised in 25 (diverticular disease, haemorrhoids and irritable bowel syndrome) and in 4 no obvious reason for the symptoms was found. This represents a predictive yield for neoplasia for a positive questionnaire of 0%. Thus, the number of investigations performed by including the questionnaire increased by 29 for no additional identification of either cancer or polyp. This represents a significant rise in investigational procedures for the programme ($p < 0.001$ X^2 test). Of the 211 individuals with 3 positive responses who were not investigated, no colonic cancer has been diagnosed after 18 months of follow-up but one patient has been identified as suffering with pancreatic cancer and has undergone surgical treatment.

DISCUSSION

Despite the high prevalence of symptoms in the population, no significant neoplastic disease in the study could be identified by the questionnaire. This may be due to the fact that the incidence of dark red blood in the stool was reported once in the 683 subjects compared with 17 in 900 for Silman's study[10]. In a similar study in Nottingham, Farrands and Hardcastle[14] have reported the use of a 5 item self-completed questionnaire in conjunction with FOB testing and

found a yield for their questionnaire of 1 polyp (P.Y = 0.8%). However, in the same individuals, FOB's detected 4 cancers and 6 polyps, constituting a false negative rate for the questionnaire of 83% (Table III).

The current more detailed questionnaire was acceptable to the public and was readily completed thus the issue of compliance as reported by Crespi[12] is not a problem compared with FOB testing. However the inclusion of the questionnaire as an adjunct to FOB testing aiming to reduce the false negative rate and false positive rates associated with FOB's, has significantly increased the number of people requiring additional investigation . This increased the running costs of the study and would further reduce the cost-effectiveness of screening compared to using FOB's alone. The yield for the questionnaire could be considered to be low because we did not investigate all individuals with only one symptom. To date no new colonic neoplasia with an 18 month follow-up has been recorded although one individual has developed obstructive jaundice secondary to cancer of the pancreas. Further the prevalence of symptoms in the current study reflects the prevalence of symptoms found in other random populations examined by Jones[15] and Thompson and Heaton[16] thus reinforcing the belief that symptom questionnaires will elicit considerable symptoms of benign disease precluding its value in the detection of symptomatic polyps or cancer.

We conclude therefore that despite the severe limitations associated with the faecal occult blood test, the addition of a symptom questionnaire to colorectal cancer screening is not viable and could seriously reduce the cost-effectiveness of such a programme.

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TABLE I

Composition of the Questionnaire

questions concerning:	Oesophagus	3
	Stomach	3
	Bowel habit	8
	Weight, appetite	4
systems:	Resp; GU; Drugs	11
	Past history	6
	Family history	2
	Epidemiological	4

TABLE II

Frequency of individual symptoms

Symptoms	No.	%
Reduced appetite	55	6.75
Wt loss, no diet	35	4.3
Difficulty swallowing	20	2.45
Food sticking	42	5.24
Heartburn	192	23.76
Nausea	101	12.48
Pain/discomfort	143	17.85
New pain	61	10.34
Bowel habit	32	4.03
Incomplete emptying	66	8.12
Altered frequency	50	6.17
Altered appetite	59	7.3
Looseness	212	26.1
Constipation	112	13.9
Blood	90	11.3
Slime	57	6.99

TABLE III

Comparison of Questionnaires for Bowel Cancer Screening

	Criteria for Investigation	No +ve	%	Finding	Predictive Yield %
Silman (10)	1 +ve response	114	12	7 polyps	16.1
Farrands (14)	1 +ve response	128	23.5	1 polyp	0.78
Chisholm	3 +ve responses	29	4.2	0	0